Table of Contents

List of Tables

List of Figures

Abbreviations

aOR	Adjusted odds ratio
APH	Antepartum haemorrhage
BMI	Body mass index
CS	Caesarean section
CI	Confidence interval
FGR	Fetal growth restriction
GDM	Gestational diabetes mellitus
GWG	Gestational weight gain
LMC	Lead maternity carer
LGA	Large for gestational age
NWH	National Women's Health
NZ	New Zealand
OR	Odds ratio
PAR	Population attributable risk
RR	Relative risk
SCOPE	Screening for pregnancy endpoints study
SGA	Small for gestational age
SGAcust	SGA defined by a customised birthweight standard.
SGAold	SGA defined by an old NZ customised birthweight model.
SGAnew	SGA defined by the new NZ customised birthweight model.
SGApop	SGA defined by a population birthweight standard
WHO	World Health Organization

THE UNIVERSITY OF AUCKLAND
SCHOOL OF GRADUATE STUDIES

Co-Authorship Form

Graduate Centre
ClockTower – East Wing
22 Princes Street, Auckland
Phone: +64 9 373 7599 ext 81321
Fax: +64 9 373 7610
Email: postgraduate@auckland.ac.nz
www.postgrad.auckland.ac.nz

This form is to accompany the submission of any PhD that contains research reported in published or unpublished co-authored work. **Please include one copy of this form for each co-authored work.** Completed forms should be included in all copies of your thesis submitted for examination and library deposit (including digital deposit), following your thesis Abstract.

Please indicate the chapter/section/pages of this thesis that are extracted from a co-authored work and give the title and publication details or details of submission of the co-authored work. Chapter 6. Ngaire H. ANDERSON, Lynn C. SADLER, Alistair W. STEWART and Lesley M.E. McCOWAN. Maternal and pathological pregnancy characteristics in customised birthweight centiles and identification of at-risk small-for-gestational-age infants: a retrospective cohort study. BJOG, 119(7), 848-856. doi:10.1111/j.1471-0528.2012.03313.x	
Nature of contribution by PhD candidate	Design of study, planning and performing analyses, interpreting data, writing manuscript
Extent of contribution by PhD candidate (%)	85

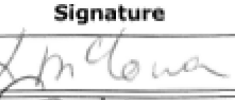
CO-AUTHORS

Name	Nature of Contribution
Prof Lesley McCowan	Design of study and analyses, interpreting data, editing manuscript
Lynn Sadler	Design of study and analyses, interpreting data, editing manuscript
Alistair Stewart	Statistical assistance, interpreting data, editing manuscript

Certification by Co-Authors

The undersigned hereby certify that:

- the above statement correctly reflects the nature and extent of the PhD candidate's contribution to this work, and the nature of the contribution of each of the co-authors; and
- in cases where the PhD candidate was the lead author of the work that the candidate wrote the text.

Name	Signature	Date
Prof Lesley McCowan		19-11-12
Lynn Sadler		3/12/2012
Alistair Stewart		16/11/12

THE UNIVERSITY OF AUCKLAND
SCHOOL OF GRADUATE STUDIES

Co-Authorship Form

Graduate Centre
ClockTower – East Wing
22 Princes Street, Auckland
Phone: +64 9 373 7599 ext 81321
Fax: +64 9 373 7610
Email: postgraduate@auckland.ac.nz
www.postgrad.auckland.ac.nz

This form is to accompany the submission of any PhD that contains research reported in published or unpublished co-authored work. **Please include one copy of this form for each co-authored work.** Completed forms should be included in all copies of your thesis submitted for examination and library deposit (including digital deposit), following your thesis Abstract.

Please indicate the chapter/section/pages of this thesis that are extracted from a co-authored work and give the title and publication details or details of submission of the co-authored work. Chapter 7. Ngaire H. ANDERSON, Lynn C. SADLER, Alistair W. STEWART, Elaine M. FYFE and Lesley M.E. McCOWAN. Independent risk factors for infants who are small for gestational age by customised birthweight centiles in a multi-ethnic New Zealand population. Australian & New Zealand Journal of Obstetrics & Gynaecology. doi:10.1111/ajo.12016	
Nature of contribution by PhD candidate	Design of study, planning and performing analyses, interpreting data, writing manuscript
Extent of contribution by PhD candidate (%)	85

CO-AUTHORS

Name	Nature of Contribution
Prof Lesley McCowan	Design of study and analyses, interpreting data, editing manuscript
Lynn Sadler	Design of study and analyses, interpreting data, editing manuscript
Alistair Stewart	Statistical assistance, interpreting data, editing manuscript
Elaine Fyfe	Interpretation of data, editing manuscript

Certification by Co-Authors

The undersigned hereby certify that:

- the above statement correctly reflects the nature and extent of the PhD candidate's contribution to this work, and the nature of the contribution of each of the co-authors; and
- in cases where the PhD candidate was the lead author of the work that the candidate wrote the text.

Name	Signature	Date
Prof Lesley McCowan	L McCowan	19-11-12
Lynn Sadler	LSadler	3/12/2012
Alistair Stewart	Stewart	16/11/12
Elaine Fyfe	EFyfe	16/11/12

THE UNIVERSITY OF AUCKLAND
SCHOOL OF GRADUATE STUDIES

Graduate Centre
ClockTower – East Wing
22 Princes Street, Auckland
Phone: +64 9 373 7599 ext 81321
Fax: +64 9 373 7610
Email: postgraduate@auckland.ac.nz
www.postgrad.auckland.ac.nz

Co-Authorship Form

This form is to accompany the submission of any PhD that contains research reported in published or unpublished co-authored work. **Please include one copy of this form for each co-authored work.** Completed forms should be included in all copies of your thesis submitted for examination and library deposit (including digital deposit), following your thesis Abstract.

Please indicate the chapter/section/pages of this thesis that are extracted from a co-authored work and give the title and publication details or details of submission of the co-authored work. Chapter 8. Anderson N, McCowan L, Fyfe E, Chan E, Taylor R, Stewart A, Dekker G, North R, on behalf of the SCOPE Consortium. The impact of maternal body mass index on the phenotype of pre-eclampsia: a prospective cohort study. BJOG 2012; DOI: 10.1111/j.1471-0528.2012.03278.x.	
Nature of contribution by PhD candidate	Design of study, planning analyses and interpreting data, writing manuscript
Extent of contribution by PhD candidate (%)	80

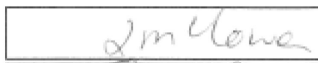
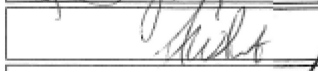
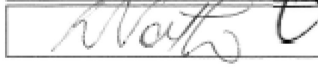
CO-AUTHORS

Name	Nature of Contribution
Prof Lesley McCowan	Design of study, planning analyses and interpreting data, editing manuscript
Elaine Fyfe	Collecting data, editing manuscript
Eliza Chan	Performing data analysis
Rennae Taylor	Collecting data, editing manuscript
Alistair Stewart	Planning analysis and interpreting data, editing manuscript
Prof Gus Dekker	Design of study, editing manuscript
Prof Robyn North	Design of study, planning analyses and interpreting data, editing manuscript

Certification by Co-Authors

The undersigned hereby certify that:

- the above statement correctly reflects the nature and extent of the PhD candidate's contribution to this work, and the nature of the contribution of each of the co-authors; and
- in cases where the PhD candidate was the lead author of the work that the candidate wrote the text.

Name	Signature	Date
Prof Lesley McCowan		10-2-12
Elaine Fyfe		10/2/12
Eliza Chan		20/02/2012
Rennae Taylor		10.2.2012
Alistair Stewart		13/2/2012
Prof Gus Dekker		13-3-12
Prof Robyn North		2014/2012

THE UNIVERSITY OF AUCKLAND
SCHOOL OF GRADUATE STUDIES

Co-Authorship Form

Graduate Centre
ClockTower – East Wing
22 Princes Street, Auckland
Phone: +64 9 373 7599 ext 81321
Fax: +64 9 373 7610
Email: postgraduate@auckland.ac.nz
www.postgrad.auckland.ac.nz

This form is to accompany the submission of any PhD that contains research reported in published or unpublished co-authored work. **Please include one copy of this form for each co-authored work.** Completed forms should be included in all copies of your thesis submitted for examination and library deposit (including digital deposit), following your thesis Abstract.

Please indicate the chapter/section/pages of this thesis that are extracted from a co-authored work and give the title and publication details or details of submission of the co-authored work.	Chapter 9. Ngaire H. ANDERSON, Lynn C. SADLER, Alistair W. STEWART, Elaine M. FYFE and Lesley M.E. McCOWAN. Ethnicity, body mass index and risk of pre-eclampsia in a multiethnic New Zealand population. Australian & New Zealand Journal of Obstetrics & Gynaecology. doi:10.1111/j.1479-828X.2012.01475.x
Nature of contribution by PhD candidate	Design of study, planning and performing analyses, interpreting data, writing manuscript
Extent of contribution by PhD candidate (%)	85

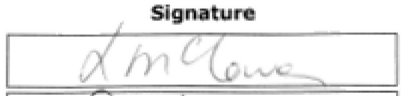
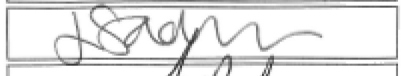
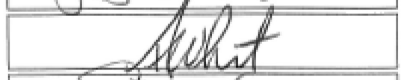
CO-AUTHORS

Name	Nature of Contribution
Prof Lesley McCowan	Design of study and analyses, interpreting data, editing manuscript
Lynn Sadler	Design of study and analyses, interpreting data, editing manuscript
Alistair Stewart	Statistical assistance, interpreting data, editing manuscript
Elaine Fyfe	Interpretation of data, editing manuscript

Certification by Co-Authors

The undersigned hereby certify that:

- the above statement correctly reflects the nature and extent of the PhD candidate's contribution to this work, and the nature of the contribution of each of the co-authors; and
- in cases where the PhD candidate was the lead author of the work that the candidate wrote the text.

Name	Signature	Date
Prof Lesley McCowan		19-11-12.
Lynn Sadler		3/12/2012
Alistair Stewart		16/11/12
Elaine Fyfe		16/11/12

THE UNIVERSITY OF AUCKLAND
SCHOOL OF GRADUATE STUDIES

Co-Authorship Form

Graduate Centre
ClockTower – East Wing
22 Princes Street, Auckland
Phone: +64 9 373 7599 ext 81321
Fax: +64 9 373 7610
Email: postgraduate@auckland.ac.nz
www.postgrad.auckland.ac.nz

This form is to accompany the submission of any PhD that contains research reported in published or unpublished co-authored work. **Please include one copy of this form for each co-authored work.** Completed forms should be included in all copies of your thesis submitted for examination and library deposit (including digital deposit), following your thesis Abstract.

Please indicate the chapter/section/pages of this thesis that are extracted from a co-authored work and give the title and publication details or details of submission of the co-authored work. Chapter 10. Ngaire H. ANDERSON, Lynn C. SADLER, Alistair W. STEWART, Elaine M. FYFE and Lesley M.E. McCOWAN. Ethnicity and risk of Caesarean section in a term, nulliparous New Zealand obstetric cohort. Australian & New Zealand Journal of Obstetrics & Gynaecology. Accepted for publication 10/11/12	
Nature of contribution by PhD candidate	Design of study, planning and performing analyses, interpreting data, writing manuscript
Extent of contribution by PhD candidate (%)	85

CO-AUTHORS

Name	Nature of Contribution
Prof Lesley McCowan	Design of study and analyses, interpreting data, editing manuscript
Lynn Sadler	Design of study and analyses, interpreting data, editing manuscript
Alistair Stewart	Statistical assistance, interpreting data, editing manuscript
Elaine Fyfe	Interpretation of data, editing manuscript

Certification by Co-Authors

The undersigned hereby certify that:

- the above statement correctly reflects the nature and extent of the PhD candidate's contribution to this work, and the nature of the contribution of each of the co-authors; and
- in cases where the PhD candidate was the lead author of the work that the candidate wrote the text.

Name	Signature	Date
Prof Lesley McCowan	L McCowan	19-11-12.
Lynn Sadler	L Sadler	2/12/2012
Alistair Stewart	A Stewart	16/11/12
Elaine Fyfe	E M Fyfe	16/11/12

Chapter 1. | Introduction

1.1. Background

Obesity and pregnancy

Obesity, which has been described as one of the most important global epidemics of modern times, is increasing in all age groups (Haslam & James, 2005; World Health Organization, 2000). The prevalence of obesity in both developed and developing countries has more than doubled over the past 30 years (World Health Organization, 2011) with far-reaching consequences. Excess adiposity is strongly associated with many common health disorders and is the fifth leading clinical risk factor for death globally (Haslam & James, 2005; World Health Organization, 2000, 2011). Reasons behind this international obesity epidemic are multifactorial and not fully understood, but major contributing factors include changes in living environments that promote obesity, i.e. the combination of low cost, energy-dense but low nutritional value foods, with more sedentary lifestyles (World Health Organization, 2000).

Globally, women generally have higher rates of overweight and obesity than men (W. P. T. James et al., 2004). In the midst of an obesity epidemic this means that a substantial proportion of all women of childbearing age in Western countries are now overweight or obese. Among women giving birth at National Women's Health (NWH), Auckland City Hospital, Auckland, New Zealand (NZ) the prevalence of overweight and obesity is 36% (National Women's Health, 2012). Obesity is an independent risk factor for many adverse pregnancy outcomes including pre-eclampsia (Cedergren, 2004; Dekker, 1999; O'Brien, Ray, & Chan, 2003), Caesarean section (CS) (Barau et al., 2006; Cedergren, 2009; Ehrenberg, Durnwald, Catalano, & Mercer, 2004; Poobalan, Aucott, Gurung, Smith, & Bhattacharya, 2009; Vahratian, Zhang, Hasling, et al., 2004), macrosomia (excess fetal growth) (Cedergren, 2004; Ehrenberg, Mercer, & Catalano, 2004) and perinatal death (Cedergren, 2004; Stephansson, Dickman, Johansson, & Cnattingius, 2001). For most adverse pregnancy outcomes there is a well-documented 'dose dependent' relationship with increasing maternal BMI (Barau et al., 2006; Cedergren, 2004). In addition, obesity during pregnancy has been shown to have epigenetic effects on fetuses independent of any adverse pregnancy outcomes (Lavebratt, Almgren, & Ekstrom, 2012). This fetal metabolic programming results in an increased chance of adult obesity and metabolic syndrome, thus perpetuating a vicious cycle. Despite these well documented risks, there are very limited local NZ data on the impact of obesity on pregnancy outcomes.

Ethnicity and pregnancy

Internationally, relationships between ethnicity and adverse pregnancy outcomes have been described, but rarely has BMI been included in these analyses (Caughey, Stotland, Washington, &

Escobar, 2005; Thomas, Paranjothy, & Royal College of Obstetricians and Gynaecologists Clinical Effectiveness Support Unit, 2001). Although rates of obesity are increasing in all populations, some ethnicities have substantially higher (and also lower) rates of overweight and obesity compared with European ethnicity (Ministry of Health, 2009a). In NZ, 72% of Māori women and 88% of Pacific women are overweight or obese compared with 55% of all women (Ministry of Health, 2009a). These national rates are reflected in the NWH obstetric population where 60% of Māori and 82% of Pacific women are overweight or obese compared with 29% of European women (National Women's Health, 2012). Conversely, only 16% of Asian women are overweight or obese in this same NWH population. Additionally, the percentage of body fat and lean body mass varies between ethnicities for the same body mass index (BMI), which further confounds the association between ethnicity, obesity and adverse pregnancy outcomes. Few local NZ studies have investigated the risk of pregnancy complications in Māori and Pacific women (or other NZ ethnicities), and rarely were these studies able to account for BMI.

1.2. Aims of this research

The broad aims of this research were to investigate the contribution of maternal obesity and ethnicity to important and common pregnancy outcomes in our local NZ obstetric population.
In particular:

- to assess the physiological and pathological impact of ethnicity and obesity on infant birthweight, including risk of small for gestational age (SGA) infants,
- to explore the similarities and differences in the clinical phenotype of pre-eclampsia among overweight and obese mothers compared with pre-eclampsia occurring in normal weight mothers,
- to investigate whether ethnicity is independently associated with pre-eclampsia after adjusting for comprehensive clinical confounders including BMI, and
- to investigate whether ethnicity is independently associated with either elective or emergency CS rates after adjusting for comprehensive clinical confounders including BMI.

1.3. Structure of thesis

This thesis begins with four background chapters that introduce and discuss the literature surrounding obesity, ethnicity and their complex interactions with pregnancy outcomes. Chapter 2 is an overview of obesity including classifications, epidemiology, pathophysiology and health consequences. This is followed in Chapter 3 by an overview of the impact of obesity on pregnancy outcomes, with a focus on infant birthweight, pre-eclampsia and CS, along with associated infant and maternal complications. Chapter 4 discusses the difficulties of defining ethnicity and describes ethnicity-related associations with both general health

outcomes and pregnancy outcomes, including infant birthweight, pre-eclampsia and CS. Associations with other confounders of ethnicity such as obesity, socioeconomic status, diet and lifestyle factors are also discussed. The final background chapter, Chapter 5, focuses specifically on infant birthweight and describes physiological and pathological influences on birthweight as well as providing further details and rationale behind customised birthweight centiles.

The body of this thesis is five manuscripts that report the research findings of individual studies. All of these manuscripts have been published in international peer-reviewed journals.

Chapter 6: 'Maternal characteristics in customised birthweight centiles' (published in the British Journal of Obstetrics and Gynaecology, 2012), is an analysis of the local NZ customised birthweight model, updated with modern data. The value of adjusting for maternal characteristics (height, weight, ethnicity and parity) in a customised birthweight model is investigated. It is hypothesised that a model including these adjustments would better detect SGA infants who are at-risk of perinatal death. This updated customised birthweight model is now in clinical use nationwide.

Chapter 7: 'Independent risk factors for customised small for gestational age infants' (published in the Australian and New Zealand Journal of Obstetrics and Gynaecology, 2012) is the first analysis of independent risk factors for infants who are SGA by customised centiles in a general obstetric cohort. It is hypothesised that, in contrast to SGA defined by population birthweight centiles, obesity would not have a protective association with SGA by customised centiles. This study also formally documents other clinical risk factors for customised SGA.

Chapter 8: 'The phenotype of pre-eclampsia in overweight and obese women' (published in the British Journal of Obstetrics and Gynaecology, 2012) is a secondary analysis of data from a prospective cohort study in healthy nulliparous women. We investigate women with pre-eclampsia, assessing how the clinical phenotype of pre-eclampsia differs by maternal BMI. It is hypothesised that obese women would be more likely to display the milder 'late-onset' phenotype of pre-eclampsia than women of normal weight.

Chapter 9: 'Ethnicity, body mass index and pre-eclampsia' (published in the Australian and New Zealand Journal of Obstetrics and Gynaecology, 2012) is an investigation into the independent impact of ethnicity on risk of pre-eclampsia. It is hypothesised that ethnicity will not be associated with risk of pre-eclampsia after comprehensive adjustment for known confounders including BMI.

Chapter 10: 'Ethnicity and Caesarean section' (published in the Australian and New Zealand Journal of Obstetrics and Gynaecology, 2013) is an investigation into the independent association between ethnicity and both elective and emergency CS, with separate analysis and adjustment for the different clinical confounders of both elective and emergency CS. It is hypothesised that Māori and Pacific women will have a lower rate of elective CS than European,

but there will be no difference in rates of emergency CS between ethnicities after comprehensive adjustment for known confounders including BMI.

These papers are followed in Chapter 11 by a summary and discussion of this body of work, an examination of the strengths and limitations of the studies, and proposals for future research.

Chapter 2. | Overweight and obesity

2.1. Introduction

Overweight and obesity can be defined as the accumulation of excess body fat that leads to impaired health (World Health Organization, 2000). At the most basic level, overweight and obesity result from an imbalance of excess energy consumed versus energy expended (Egger & Swinburn, 1997) however the meteoric rise in global obesity prevalence among developed and developing countries alike suggests the aetiology is infinitely more complex. In 2008 the World Health Organization (WHO) estimated that more than 1.4 billion adults were overweight and more than one-in-ten of the world's adult population was obese. Overweight and obesity is now the fifth leading risk factor for death globally, and 44% of the worldwide burden of diabetes, 23% of ischaemic heart disease burden and between 7% and 41% of the burden of certain cancers has been attributed to obesity (World Health Organization, 2012c). Obesity is ultimately preventable.

2.2. Definitions

Excess adiposity can be classified into subgroups depending on the presumed underlying aetiology. The vast majority of obese individuals belong to the subgroup of polygenic or common obesity which affects the general population. Monogenic obesity (extremely severe obesity in the absence of developmental delay) and syndromic obesity (obesity with mental handicap, dysmorphic features, and developmental abnormalities) are rare, and will not be considered further in this thesis (B. M. Herrera & Lindgren, 2010).

Overweight and obesity can be defined respectively as an increased and excess risk of adiposity-related disease (World Health Organization, 2000). Various anthropometric measurements can be used to classify excess body-fat, and include body mass index (BMI, or weight to height ratio), waist circumference, waist to hip ratio (WHR), as well as estimates of body fat percentage obtained through skinfold thickness measurements, bioelectrical impedance analysis and dual energy X-ray absorptiometry (DXA).

BMI, calculated as weight in kilograms divided by height in metres squared (kg/m^2), is an easily obtained measure that is independent of age, sex or ethnicity and has a high correlation with adiposity (Gray & Fujioka, 1991; Kuczmarski & Flegal, 2000). BMI cannot however differentiate between weight associated with muscle and weight associated with fat, and so cannot quantify total body adiposity or assess regional body fat distribution (World Health Organization, 2000). Despite this, it remains the most widely used measure for estimating obesity prevalence in population studies. The classification of BMI into underweight, normal, overweight and obese categories allows for meaningful comparisons between populations as well as the identification

Table 2.1. Classification of body mass index (BMI) by World Health Organization criteria

Classification	BMI (kg/m^2)	Risk of adiposity-related comorbidities
Underweight	<18.5	Low (but risk of other problems increased)
Normal range	18.5-24.9	Average
Overweight:	≥25.0	
Preobese	25.0-29.9	Increased
Obese class I	30.0-34.9	Moderate
Obese class II	35.0-39.9	Severe
Obese class III	≥40.0	Very severe

of at-risk individuals. The most widely accepted international classification of BMI for adults was developed by the WHO using the criteria of adiposity-related risk of comorbidities and premature mortality, Table 2.1 (World Health Organization, 2000).

This WHO BMI classification was developed primarily using data from European populations (WHO/IASO/IOTF, 2000; World Health Organization, 2000) however it has subsequently been recognised that adiposity-related health risks are increased at lower BMIs in Asian populations. For a given BMI, body 'fatness' or adiposity levels vary between ethnicities, e.g. Polynesian adults have a lower percentage of body fat (i.e. a greater lean body mass) than Europeans for the same BMI (Deurenberg, Yap, & van Staveren, 1998; Swinburn, Ley, Carmichael, & Plank, 1999), and conversely Asian adults have a higher percentage of body fat than Europeans for the same BMI (Deurenberg, Deurenberg-Yap, & Guricci, 2002). In Asian populations this corresponds to an increased risk of cardiovascular disease, diabetes and adiposity-related risk factors such as hypercholesterolaemia and hypertension, occurring at BMIs lower than the WHO cut-off for overweight (25kg/m^2) (Deurenberg-Yap & Deurenberg, 2003; Ko, Chan, Cockram, & Woo, 1999) (see also section 4.3 below). As a result, the WHO has recommended additional BMI criteria for Asian populations that reflect this increased risk at lower BMIs, Table 2.2 (World Health Organization expert consultation, 2004). Adjusted criteria have also been proposed for Polynesian adults that reflect a lower percentage body fat and increased lean body mass compared to European adults, Table 2.2 (Swinburn et al., 1999; WHO/IASO/IOTF, 2000).

Table 2.2. Ethnic-specific body mass index (BMI) categories

Classification	BMI (kg/m^2)			Risk of adiposity-related comorbidities[1]
	Asian/Indian	European	Polynesian	
Underweight	<18.5	<18.5	<18.5	Low (but risk of other problems increased)
Normal	18.5 - 23.4	18.5 - 24.9	18.5 - 25.9	Average
Overweight	23.5 - 27.4	25.0 - 29.9	26.0 - 31.9	Increased
Obese	≥27.5	≥30.0	≥32	High

Waist circumference and WHR are both measures of visceral or abdominal adiposity. Visceral adipose tissue is body fat located within the abdominal cavity and is more 'metabolically active' than subcutaneous adipose tissue (Despres & Lemieux, 2006). Individuals with abdominal obesity are at greater risk than those with subcutaneous obesity of developing metabolic syndrome, a syndrome of abnormal blood lipids, inflammation, insulin resistance and an increased risk of cardiovascular disease (Despres & Lemieux, 2006; Eckel, Grundy, & Zimmet, 2005; Müller et al., 2012). Both waist circumference and WHR correlate well with BMI (Lean, Han, & Morrison, 1995) and total body-fat (Han, Lean, & Seidell, 1996), and are associated with cardiovascular disease risk factors such as hypercholesterolaemia and hypertension independent of BMI (Shen et al., 2006; S. Zhu et al., 2002). Waist measurements however have not been validated for use in pregnancy, including in early pregnancy.

Estimations of adiposity and body fat distribution using skinfold and bioelectrical impedance assessments are also well established. These methods allow for direct assessment of an individual's fat percentage however they are not feasible for population-based assessments of adiposity due to resource implications including equipment and training. The current research standard for body composition analysis, including fat mass assessment, is DXA (Albanese, Diessel, & Genant, 2003; Volgyi et al., 2008). This procedure involves a single whole body X-ray scan that calculates fat mass by subtracting lean mass and bone mineral mass from total body mass, Figure 2.1 (Albanese et al., 2003; Pietrobelli, Formica, Wang, & Heymsfield, 1996). This method has been used to assess differences in fat mass percentages between ethnicities (Swinburn et al., 1999; WHO/IASO/IOTF, 2000) and between sexes (R. W. Taylor, Grant, Williams, & Goulding, 2010) however, as with skinfold and bioelectrical impedance assessment, DXA is impractical for population-based assessments of adiposity.

[1] Risk of comorbidities in Polynesian populations is presumed based on equivalent fat mass to European (Swinburn et al., 1999)

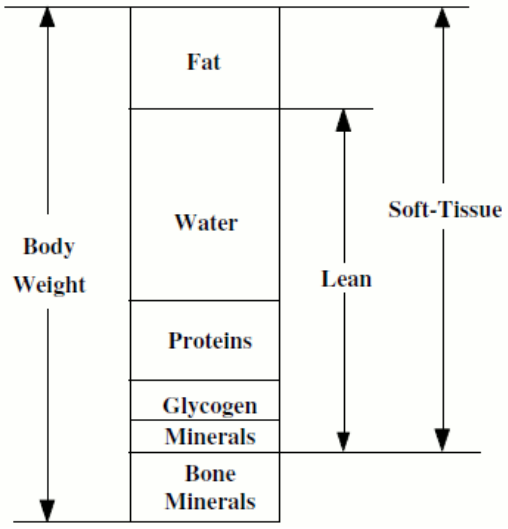


Figure 2.1. Dual energy X-ray absorptiometry (DXA) two-component soft tissue model. Reproduced from American Journal of Physiology, Pietrobelli et al. (1996), permission not required for use.

2.3. Epidemiology

Over the last three decades obesity has transformed from a disease of wealthy industrialised nations, into a global epidemic with escalating prevalence in both developed and developing countries. International estimates using WHO BMI criteria (Table 2.1) suggest the worldwide prevalence of obesity doubled between 1980 and 2008 from 5% to 10% in men, and 8% to 14% in women (Finucane et al., 2011). Over this same time frame, obesity rates in New Zealand (NZ) women have more than doubled from 11% to 26%, and currently over half of NZ women (55%) are overweight or obese (Ministry of Health, 2008, 2009a). Of the Organisation for Economic Co-Operation and Development (OECD) countries, NZ women rank fourth highest in rates of overweight or obesity, Figure 2.2 (Sassi, 2010).

Rates of obesity also vary substantially by ethnicity (Colin Bell, Adair, & Popkin, 2002; W. P. T. James et al., 2004; Ministry of Health, 2008). In NZ, the highest rates of obesity (BMI ≥30kg/m^2) occur in Māori and Pacific women (43% and 66% respectively), while Asian (including Chinese and Indian) women have the lowest rate at 12% (Ministry of Health, 2009a). In developed countries like NZ, obesity is also strongly associated with poverty (Popkin & Gordon-Larsen, 2004; Sassi, 2010) and Māori and Pacific peoples have the highest levels of socio-economic deprivation of all NZ ethnicities (Ministry of Health, 2010).

As the accumulation of excess adiposity generally occurs gradually, obesity has previously been more prevalent among older adults (Ogden, Carroll, Kit, & Flegal, 2012; Swinburn et al., 2011; World Health Organization, 2000). Increasingly however, obesity is being observed at younger ages, with steadily rising rates of overweight and obesity observed among children and adolescents, Figure 2.3 (Popkin & Gordon-Larsen, 2004; Swinburn et al., 2011; World Health Organization, 2000). In a maternity setting, this trend of excess adiposity in young people means

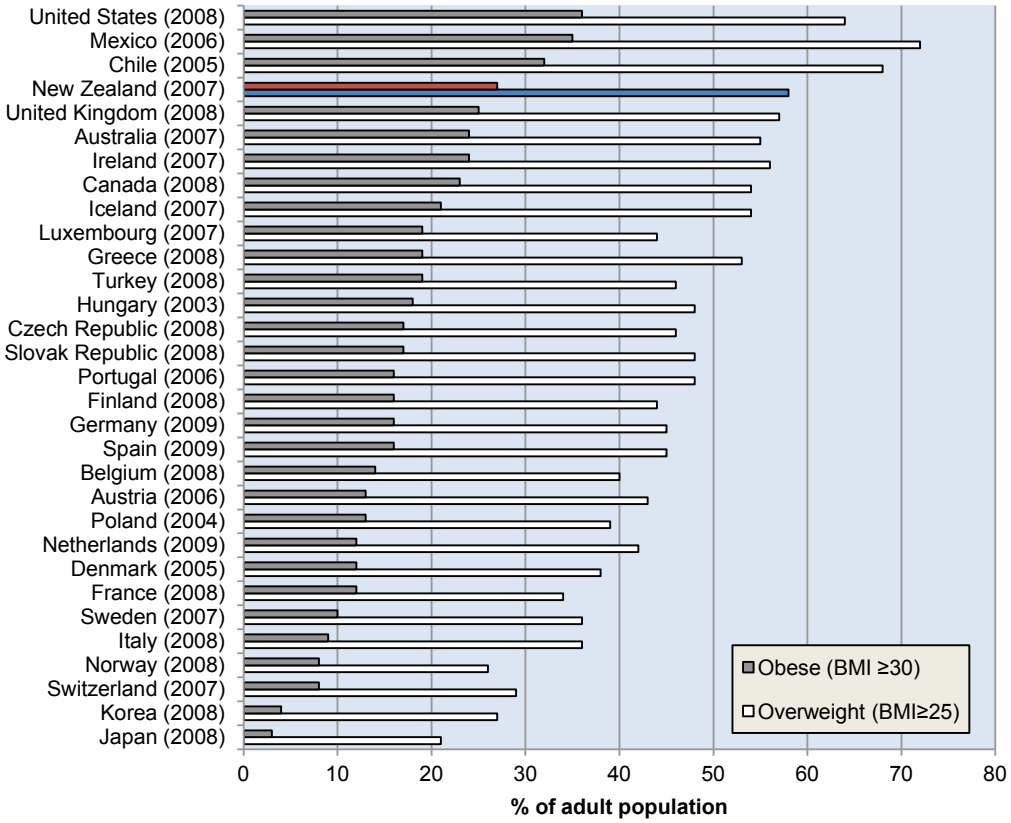


Figure 2.2. Female obesity and overweight in OECD countries. Adapted from figure 2.1 'Obesity and overweight in OECD countries' from OECD (2010), Obesity and the Economics of Prevention: Fit not Fat, OECD Publishing. http://dx.doi.org/10.1787/9789264084865-en.

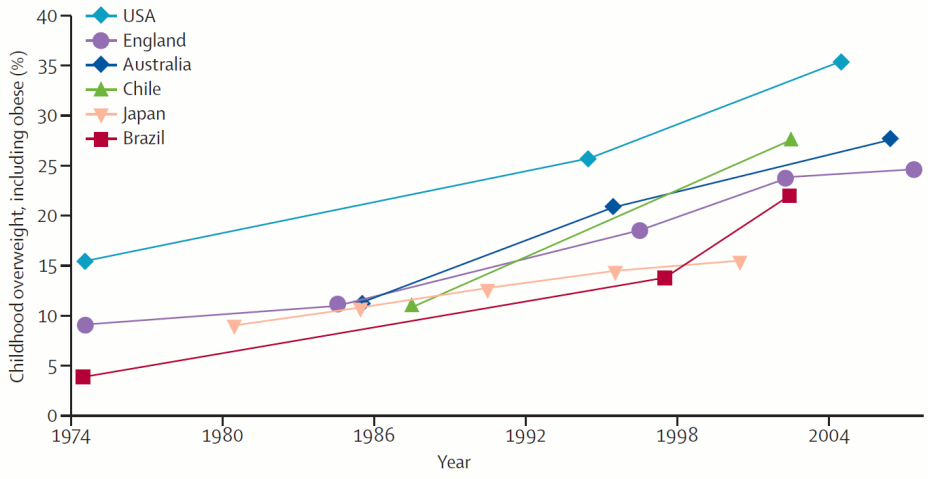


Figure 2.3. Estimates of percentage of childhood population overweight (including obese) in a selection of countries. Reprinted from The Lancet, Vol 378, Swinburn et al. The global obesity pandemic: shaped by global drivers and local environments, 804-14, Copyright 2011, with permission from Elsevier.

women in their reproductive years are not only more likely to be obese, but are also more likely to enter pregnancy with obesity-related chronic disease complications such as diabetes and hypertension (Boney, Verma, Tucker, & Vohr, 2005; Flynn, 2012).

2.4. Aetiology

The underlying aetiology of excess adiposity can be reduced to an excess of energy consumed relative to the amount of energy expended. However behind this simplistic explanation are a vast array of environmental, biological, physiological and behavioural factors that impact on an individual's risk of becoming overweight or obese, Figure 2.4. In contrast to the widely held belief, obesity is not simply a result of overindulgence in food or a lack of physical activity, but instead results from a complex interaction between an individual and their environment.

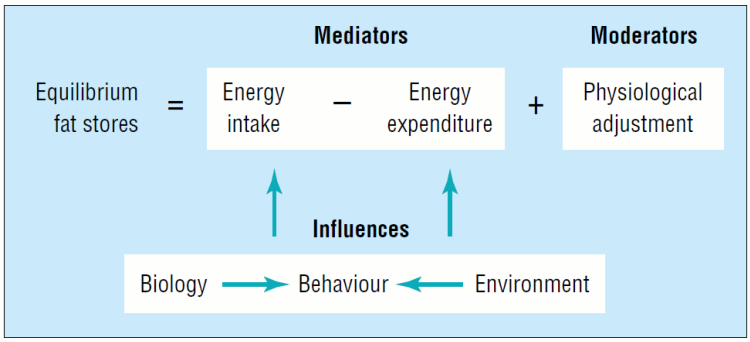


Figure 2.4. An 'ecological' paradigm for understanding over-fatness and obesity. Reproduced from BMJ, Egger et al. 315,477-80, 1997 with permission from BMJ Publishing Group Ltd.

2.4.1. Environmental factors - diet and physical activity

Worldwide shifts in patterns of diet and physical activity have been observed over the last 30 years, contemporaneous with the obesity epidemic. Advances in food manufacturing, processing and retail supply in Western societies have lead to increases in food supply to consumers. This abundance of food has been identified as a dominant driver of population weight gain in both the United States (USA) and the United Kingdom (UK) (Scarborough et al., 2011; Swinburn, Sacks, & Ravussin, 2009). At the same time, food technology has progressed to the point where products can now have almost any combination of taste, appearance and nutritional content. Food is now produced in a way that consumers cannot rely on sensory cues to appreciate the energy content of what is eaten (World Health Organization, 2000). In addition, the most palatable products tend to be foods that are high in salt, fat and sugar (W. P. T. James, 2008; World Health Organization, 2000), and subsequently these are the foods preferentially manufactured and marketed.

The consumption of dietary fats appears to be extremely important in the regulation of energy intake and body weight (Poppitt & Prentice, 1996). As dietary fats have more than twice the energy per unit weight than either protein or carbohydrate, a small quantity of food rich in fat has a very high energy content. In addition, fat is highly palatable and has a limited ability to suppress appetite compared to carbohydrate and protein-rich foods (Drewnowski, 1998; World Health Organization, 2000). As a result, processed foods that are designed to be palatable, including being high in fat and energy dense, can easily lead to passive overconsumption of

excess energy (W. P. T. James, 2008; Popkin & Gordon-Larsen, 2004; Poppitt & Prentice, 1996). As even a small excess of daily energy intake can lead to large increases in body weight over a long time period (see section 2.4.5 below), this unconscious or passive overconsumption of energy can be an insidious contributor to obesity.

Changes in food manufacturing and supply have occurred simultaneously with a decline in physical activity (Haslam & James, 2005). Modern conveniences at home and at work such as private transport, electronic appliances and mechanisation of heavy physical labour, along with increasingly sedentary work and leisure activities dominated by television and computers, have lead to reductions in routine daily physical exertion (Church et al., 2011; W. P. T. James, 2008; Prentice & Jebb, 1995; Simmons, Jackson, Swinburn, & Yee, 1996). Physical activity not only increases energy expenditure as an important component of body weight regulation, but also improves mobilisation of fat stores, provides short-term suppression of appetite (World Health Organization, 2000), as well as having beneficial effects on cardiovascular health independent of any impact on weight (Hainer, Toplak, & Stich, 2009). Conversely, a low level of physical activity is predictive of substantial weight gain over time (Rissanen, Heliovaara, Knekt, Reunanen, & Aromaa, 1991).

The combination of an abundant supply of convenient, energy dense processed foods and decreasing physical activity has been described as an 'obesogenic' environment, i.e. an environment that promotes and subsequently maintains excess adiposity (Haslam & James, 2005; World Health Organization, 2000).

2.4.2. Biological factors

Obesity is inexorably related to biological factors, however the underlying genetics of obesity is complex and poorly understood. Estimates suggest that approximately 50% of the variation in bodyweight in adults can be explained by heritable traits (Haslam & James, 2005; World Health Organization, 2000), but in order for heritable traits to be fully expressed there must also be a favourable environment. In the case of obesity an attractive but unproven hypothesis is that obesity-related genetic traits once provided an evolutionary advantage by allowing efficient storing of nutrient energy in times of food shortage, however in an environment where food is plentiful these same traits are maladaptive and detrimental (B. M. Herrera & Lindgren, 2010). This 'thrifty gene' hypothesis is supported by observations in indigenous populations in both the USA and Australia, who develop very high rates of obesity and related metabolic complications when exposed to a more affluent and sedentary 'Western' lifestyle. These indigenous groups may therefore possess a genetic predisposition to obesity that is only expressed when exposed to an obesogenic environment (World Health Organization, 2000). Conclusions about ethnicity and genetic susceptibility to obesity need to be viewed with caution, as obesity is also strongly associated with poverty, and indigenous populations tend to live in the poorest communities of

industrialised nations (Ministry of Health, 2010; Stronks & Kunst, 2009; Ujcic-Voortman, Bos, Baan, Verhoeff, & Seidell, 2011).

Two of the major biological factors influencing body weight and composition are gender and age. In women, sex hormones have been found to influence appetite throughout the menstrual cycle with the lowest food intake occurring when estrogen levels are high (peri-ovulatory), and the highest food intake when progesterone levels are high (premenstrual) (Asarian & Geary, 2006). In pregnancy, appetite increases early under the influence of progesterone in order to encourage energy storage ready for future demands (Augustine, Ladyman, & Grattan, 2008; Landau, 1983). Women also tend to accumulate body fat in a peripheral distribution and have a higher percentage body-fat to muscle mass ratio than men for the same BMI, while men, under the influence of testosterone, accumulate fat in an abdominal or visceral distribution (R. W. Taylor et al., 2010; J. C. K. Wells, 2007). Ageing, in contrast, affects men and women in similar ways, with significant decreases in lean body mass along with increases in fat mass and overall BMI in both sexes (Guo, Zeller, Chumlea, & Siervogel, 1999). Daily energy expenditure also decreases with ageing due to a progressive decline in overall muscle mass along with decreased physical activity, predisposing to the development of obesity unless there is a corresponding decrease in food intake (Poehlman, 1992).

Hormones other than sex hormones also impact on the development of obesity. The identification of the *ob* gene and its hormonal product leptin was initially heralded as a possible key to identifying the genetic basis of obesity (Y. Zhang et al., 1994). Leptin is an adipocytokine (cell-to-cell signalling molecule produced by fat cells, i.e. adipocytes) that has actions in the central nervous system to suppress appetite and reduce food intake. Circulating leptin levels are proportional to fat mass, with obese individuals having elevated leptin, suggesting also that central leptin resistance may be a contributing factor to the development of human obesity (Considine et al., 1996). Regardless of adiposity, leptin levels drop during fasting providing a strong stimulus to eat and conserve energy, protecting against weight loss (M. W. Schwartz, Woods, Porte, Seeley, & Baskin, 2000).

Insulin has also been identified as an adiposity-signalling hormone, with basal insulin levels also corresponding to the degree of adiposity (Park & Bloom, 2005; M. W. Schwartz et al., 2000). Similar to leptin, insulin has been found to have central nervous system receptors in brain areas that control energy homeostasis, and obese individuals have a tendency to insulin resistance. Specific insulin receptor defects have also been found that result in increased food intake and subsequent adiposity (Park & Bloom, 2005). Further investigations have shown that the relationship between leptin, insulin and obesity is complex, and discoveries of multiple heritable genetic obesity traits have reinforced the polygenic nature of obesity (Gonzalez-Bulnes & Ovilo, 2012; B. M. Herrera & Lindgren, 2010).

2.4.3. Epigenetics - the interaction between biology and the environment

Epigenetic mechanisms have been described that link the early life environment with adult obesity. Epigenetics is the heritable alteration of gene expression that occurs through cellular processes such as DNA methylation and histone modification, changing the cellular phenotype without modification of the underlying DNA sequence (Lavebratt et al., 2012). These cellular changes occur during a critical period of developmental 'plasticity', namely fetal or early infant life, when a single genotype has the potential to give rise to a range of phenotypes in response to different environmental influences (Chernausek, 2012). Epigenetics can therefore be considered the link between genes and the environment (Lavebratt et al., 2012; Milagro, Mansego, De Miguel, & Martinez, 2012).

Epigenetic characteristics were observed by Barker et al in the 1980s when small infant size at birth was correlated with adult death from ischaemic heart disease (Barker, Winter, Osmond, Margetts, & Simmonds, 1989). The Barker hypothesis theorised that adverse environmental factors in early life interrupted normal growth and development, leading to an adult phenotype predisposed to cardiovascular disease (Barker, 1995). Abnormal fetal or infant growth (a surrogate for intrauterine environmental influences) has now been linked with many adult diseases including type 2 diabetes mellitus, cardio- and cerebro- vascular disease and obesity in what has been named the developmental origins of health and disease (DoHAD) (Barker, 2004; Gillman, 2005).

Adult obesity has been associated with both under- and over-nutrition *in utero*, as indicated by the 'U-shaped' association observed between birthweight and later obesity (Curhan et al., 1996; Gluckman & Hanson, 2008). Although much previous research was focussed on small infants, more recently there has been a move to investigate large for gestational age (LGA) infants and the effect of fetal over-nutrition on long term health. Fetal nutrient excess can occur in pregnancies affected by both diabetes and obesity. As diabetic mothers are also more likely to be obese, it is difficult to separate the relative contributions of obesity and diabetes to fetal nutrition, however increasing maternal BMI has been independently associated with greater fetal growth (Ehrenberg, Mercer, et al., 2004; Makgoba, Savvidou, & Steer, 2012). Infants born LGA and exposed to an intrauterine environment of diabetes or maternal obesity are at increased risk of childhood obesity and metabolic syndrome (Boney et al., 2005). (see also section 3.4.1.1 below)

In addition to *in utero* environmental influences, the early postnatal environment has been shown to have epigenetic influences on risk of obesity. Small infants who subsequently have 'catch-up' growth show an increased risk of adult obesity (Ong, 2006), particularly when associated with formula feeding (Singhal, 2006). Infants who are breast-fed have lower rates of metabolic syndrome including obesity than formula-fed infants, suggesting the nutritional

environment associated with formula feeding may introduce a detrimental epigenetic change (C. G. Owen, Martin, Whincup, Smith, & Cook, 2005; Singhal, 2006).

Although the environment and biological factors interact to have a considerable impact on the variation in adult bodyweight between individuals, human behaviour still has a substantial controlling influence on the development of obesity.

2.4.4. Behaviour

Eating is a pleasurable and social activity, and the initiation of a meal in humans is often a cognitive decision without physiological signals such as hunger. Environmental cues such as time of day, food advertising and social situations can be strong signals to eat, even in the presence of satiety and replete energy stores (Berthoud, 2006).

The palatability of food is one of the most important influences on behaviour (Berthoud, 2006; W. P. T. James, 2008; World Health Organization, 2000). Food that is highly palatable tends to promote consumption at a higher rate and increases hunger between meals, resulting in overall increased energy consumption. Highly palatable food tends to be energy dense, high fat and sweet in taste. In addition, the pleasure associated with food can lead to behavioural reinforcement, encouraging further overconsumption (Berthoud, 2006; World Health Organization, 2000).

Additional influences on behaviour include the overwhelming array of food cues in the modern environment (Herman & Polivy, 2008; W. P. T. James, 2008). Food is perpetually advertised, is easily available with minimal effort, and many traditional societal activities are based around food (e.g. birthdays, weddings, religious and holiday celebrations etc). The food industry specifically targets these emotional and behavioural responses to food to sell their products, and children are particularly vulnerable (Hastings et al., 2003; W. P. T. James, 2008).

The cultural environment also has a substantial influence on both food intake and physical activity patterns (World Health Organization, 2000). Cultural behaviours are learned from childhood, and are strong determinants of food choice. Traditional foods may be high in fat and sugar, and social pressures may require eating at gatherings in order not to appear ‘rude’. Cultures also vary in the expectation of physical activity for leisure. As daily physical activity has decreased with modern conveniences, cultural attributes have lead to sedentary lifestyles for some, while others maintain a vigorous leisure lifestyle consistent with cultural expectations (World Health Organization, 2000). Cultural attitudes also influence body image and overall acceptability of weight gain, for example a large body size is a positive attribute for Tongan women, but small body size is ideal for Japanese women (Swinburn et al., 2011).

Behaviours are the result of a complex interplay between the environment, emotions, habits and learned experiences. Cognitive factors (i.e. conscious control) can ultimately overcome learned behaviours, however for most individuals food behaviour is dictated by subconscious and

automatic responses (Berthoud, 2006; Egger & Swinburn, 1997; World Health Organization, 2000).

2.4.5. Physiology

Food intake is normally tightly regulated to match both short- and long-term energy requirements. However it takes only a small increase in daily energy consumption to initiate weight gain; an excess of only 40-80kJ (10-20kcal) per day, i.e. less than 1% of normal daily intake, can lead to a weight gain of 0.5-1kg per year (Bjorntorp, 1997; Haslam & James, 2005). This is the equivalent energy contained in half an apple, or expended by 10 minutes of low intensity exercise (e.g. walking). As weight gain continues, particularly if gradual, changes occur in body weight regulatory mechanisms that allow physiologic adaptation to the higher weight (W. P. T. James, 2008). This adaptation seems to be progressive, as despite the increasing basal metabolic energy expenditure associated with a higher bodyweight, weight gain continues (W. P. T. James, 2008). Subsequent weight loss is actively resisted despite excess energy storage, via acute physiological hormonal and autonomic nervous system mechanisms and metabolic adaptations that simulate mild starvation (W. P. T. James, 2008; Prentice et al., 1991). In general, human physiology seems to defend against weight loss, while tolerating a positive energy balance (World Health Organization, 2000).

The underlying physiological mechanisms that are responsible for regulation of body weight are complex and poorly understood, but involve numerous hormonal signalling mechanisms originating from the gut, pancreas and adipose tissue that feedback to the hypothalamus, brain stem and autonomic nervous system (Coll, Yeo, Farooqi, & O'Rahilly, 2008; Park & Bloom, 2005; World Health Organization, 2000). These signals regulate appetite and food intake, but are heavily modulated by higher brain functions including behaviour and conscious control.

2.5. Consequences of obesity

The consequences of obesity are far-reaching, and impact on nearly all aspects of health and disease. Obesity-related metabolic or inflammatory changes predispose to disease in nearly all organ systems, but obesity also impacts on the ability of an individual to function within society whether that is due to illness, social prejudice or physical limitations (World Health Organization, 2000).

Adipose tissue has a primary purpose to regulate storage and release of lipids and glucose however it is also a highly active endocrine and paracrine organ. Adipocytes produce bioactive mediators (adipocytokines) that not only regulate body weight, but also influence reproductive and cardiovascular functions, immunity, inflammation and coagulation. Excess adipose tissue causes perturbations in the normal functioning of these systems which underpins the

pathophysiology of obesity-related complications (Prins, 2002; Van Gaal, Mertens, & De Block, 2006; World Health Organization, 2000).

2.5.1. Insulin resistance

Insulin resistance is a predominant feature of obesity. Insulin is the principal regulator of glucose homeostasis by stimulating glucose uptake in adipose tissue and skeletal muscle, preventing liver release of glucose as well as suppressing adipocyte release of lipid stores (lipolysis) (Rosen & Spiegelman, 2006). Insulin also has multiple other peripheral and central regulatory roles including appetite, body weight and growth. The exact process by which excess adiposity leads to insulin resistance is unclear, but it is likely to involve complex interactions between various systems, some of which are outlined below.

Impairment of non-esterified fatty acid (NEFA) metabolism is considered to be a major contributor to insulin resistance (Callaway, O'Callaghan, & McIntyre, 2009; Despres & Lemieux, 2006; Rosen & Spiegelman, 2006). The release of NEFA from adipocytes in individuals with a normal body weight and normal insulin sensitivity is highly regulated with the amount released being directly proportional to energy requirements. Hypertrophic adipocytes in obese individuals however have an intrinsic insulin resistance, impairing the anti-lipoytic actions of insulin resulting in excess NEFA release (Despres & Lemieux, 2006; Van Gaal et al., 2006). NEFA consequently stimulates the hepatic production of both glucose (gluconeogenesis) and lipids (Callaway et al., 2009; Despres & Lemieux, 2006; Eckel et al., 2005). As part of normal glucose metabolism, NEFA is primarily released during fasting when circulating glucose and insulin is low, acting to inhibit skeletal muscle glucose uptake and promote hepatic glucose output, preserving glucose for cerebral metabolism (Rosen & Spiegelman, 2006). In the obese individual, excess NEFA promotes hyperglycaemia, leading to increased pancreatic insulin secretion, hyperinsulinaemia and insulin resistance. This vicious cycle is compounded by the lipotoxic and glucotoxic effects of elevated NEFA and glucose on pancreatic β-cells (that produce and secrete insulin) which can ultimately lead to β-cell failure and type 2 diabetes (Rosen & Spiegelman, 2006; Van Gaal et al., 2006).

Release of NEFA from adipocytes can also be directly stimulated through the action of pro-inflammatory cytokines such as tumour necrosis factor-α (TNF-α) and interleukin-6 (IL-6). As adipocytes release pro-inflammatory cytokines in response to hypertrophy, this leads to a further vicious cycle resulting in hyperglycaemia and insulin resistance. These same pro-inflammatory cytokines also have direct actions to impair cellular insulin signalling (Hotamisligil, 2006; Tilg & Moschen, 2006) while other adipocytokines such as adiponectin and leptin also alter insulin metabolism. Adiponectin, which has insulin sensitising actions, is suppressed in obesity, while elevated leptin is associated with insulin resistance (Rosen &

Spiegelman, 2006; Tilg & Moschen, 2006; Van Gaal et al., 2006). Insulin resistance is therefore tightly linked with adipose tissue production of adipocytokines and inflammation.

2.5.2. Inflammation/ immunity

Obesity is a state of chronic inflammation (Hotamisligil, 2006; Tilg & Moschen, 2006). While it is unclear whether inflammatory processes play a causal role in obesity, it is well established that the systemic inflammation that results from the release of pro-inflammatory cytokines from adipose tissue, contributes to the development of obesity-related complications such as metabolic syndrome, cardiovascular disease and type 2 diabetes, Figure 2.5 (Hotamisligil, 2006; Van Gaal et al., 2006).

The pro-inflammatory cytokines released from hypertrophic adipose tissue have multiple actions, including stimulating the release of the inflammatory acute phase reactant C-reactive protein (CRP) from hepatocytes. Low grade elevations of CRP in obesity have been linked through epidemiological studies to coronary artery disease (Van Gaal et al., 2006), and laboratory studies have confirmed that circulating TNF-α and CRP directly impair endothelial function and are likely to play a role in the pathogenesis of atheromatous plaques, Figure 2.5 (Despres & Lemieux, 2006; R. N. Taylor, Davidge, & Roberts, 2009; Van Gaal et al., 2006).

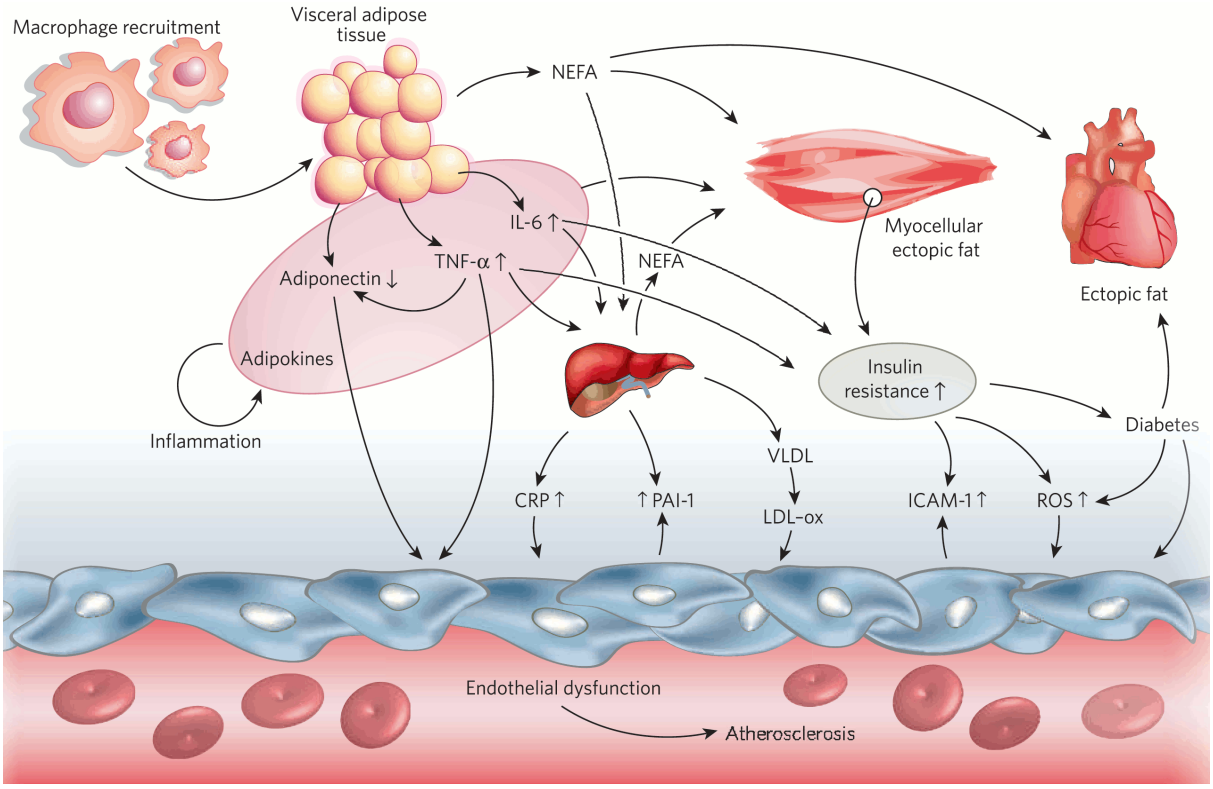


Figure 2.5. Adipose tissue as a mediator of the complications of obesity. (Adapted by permission from Macmillan Publishers Ltd: Nature, (Van Gaal et al., 2006) copyright 2006). NEFA, non-esterified fatty acids; TNF-α, tumour necrosis factor-α; IL-6, interleukin 6; CRP, C-reactive protein; PAI-1, plasminogen activator inhibitor-1; VLDL, very low density lipoprotein; LDL-ox, oxidised low density lipoprotein; ICAM-1, intercellular adhesion molecule-1: ROS, reactive oxygen species.

Inflammation is also a pivotal part of immunity and obese individuals have an alteration of immune function (Callaway et al., 2009; Hotamisligil, 2006; Tilg & Moschen, 2006). Chronic inflammation impairs the functioning of both the innate (non-specific) and adaptive (specific, e.g. antibody mediated) immune systems and is closely related to adipocytokine actions. Adiponectin (suppressed in obesity) reduces inflammation through suppression of TNF-α release, but also has direct actions that suppress phagocytosis and some adaptive immune responses. In concert, leptin (increased in obesity) has pro-inflammatory actions along with increased adaptive immune responses (Tilg & Moschen, 2006). Obesity therefore is a disease of chronic low-grade inflammation and altered immune responsiveness, which contributes to the development of obesity related diseases, including potentially the relationship between obesity and some malignancies (Tilg & Moschen, 2006).

2.5.3. Oxidative stress and endothelial dysfunction

Oxidative stress is an imbalance between the production and breakdown of reactive oxygen species (ROS), and has been theorised as a link between obesity, insulin resistance and endothelial dysfunction. Whether oxidative stress is a direct result of obesity, or results from the associated complications of obesity such as insulin resistance is unclear, but there is a strong association between increasing adiposity and increasing oxidative stress (Ceriello & Motz, 2004).

ROS typically form as a natural by-product of normal oxygen metabolism, but they also have roles in cell signalling and immunity. ROS can cause severe cellular damage, however cells have multiple inbuilt defensive mechanisms including the production of antioxidants. The oxidative stress that arises from excess ROS results in damage to epithelial cells through DNA, RNA or protein destruction. This damage interrupts normal function and impairs multiple endothelial-mediated processes including the regulation of regional blood flow, blood pressure and coagulation (Pearson, 2000). Oxidative stress is manifested by increased levels of plasminogen activator inhibitor-1 (PAI-1, an inhibitory protein required for fibrinolysis with pro-inflammatory properties) and intercellular adhesion molecule-1 (ICAM-1, an endothelial activator and marker of endothelial dysfunction). Excess ROS formation and subsequent oxidative stress occurs as a direct result of insulin resistance and dyslipidaemia, both of which are also present in obesity (Van Gaal et al., 2006).

As previously described, inflammatory mediators also impair endothelial function. The action of TNF-α and IL-6 on hepatocytes not only leads to the production of endothelial-damaging CRP, but also PAI-1 and very low density lipoprotein (VLDL) (Van Gaal et al., 2006). Increased VLDL in the presence of excess ROS leads to the generation of oxidised low density lipoprotein (LDL) which are associated with the formation of atherosclerotic lesions, Figure 2.5 (Kita et al., 2001; Ross, 1999; Van Gaal et al., 2006). Pro-inflammatory cytokines, along with free fatty acids, also

reduce endothelial production of nitric oxide, which inhibits endothelial-mediated vasodilation (resulting in peripheral vasoconstriction), a possible mechanism contributing to the development of hypertension in obesity (Pearson, 2000).

Alterations in prothrombotic factors and dyslipidaemia also contribute to endothelial dysfunction. Obesity is a prothrombotic state, with increased PAI-1 released from both hepatocytes, and endothelial cells. In addition, adipocytokines and NEFA stimulate the release of fibrinogen from liver and adipocytes, creating a prothrombotic milieu (Callaway et al., 2009; Prins, 2002).

2.5.4. Dyslipidaemia

The dyslipidaemia of obesity consists of elevated VLDL, LDL and total cholesterol, elevated triglycerides and reduced high density lipoprotein (HDL) cholesterol. Insulin resistance results in excess NEFA delivered to the liver, particularly from visceral adipocytes, and causes increased production of the liver enzyme microsomal triglyceride transfer protein (MTP) along with decreased degradation of lipoprotein apoB-100. This combination of processes results in increased production of VLDL by hepatocytes which also has reduced clearance in the presence of insulin resistance (Despres, 1994; Eckel et al., 2005; Van Gaal et al., 2006; World Health Organization, 2000). Excess VLDL then interacts with circulating LDL leading to the formation of small dense LDL particles which are prone to oxidation. These LDL particles are preferentially taken up by macrophages, creating foam cells (lipid-laden macrophages) which are implicated in the pathogenesis of atherosclerotic lesions (Eckel et al., 2005; Kita et al., 2001; Van Gaal et al., 2006).

Low levels of HDL cholesterol are risk factors for cardiovascular disease and mortality (P. W. Wilson, Abbott, & Castelli, 1988). HDL particles transport peripheral cholesterol, including from foam cells, to the liver for re-use or secretion into bile. In obesity the production of HDL cholesterol is reduced through decreased hepatocyte production in the presence of insulin resistance. In addition circulating HDL cholesterol is modified by excess VLDL and triglycerides to small dense HDL particles which are then preferentially cleared from the circulation. (Despres, 1994; Van Gaal et al., 2006).

2.5.5. Hypertension

Hypertension occurs in obesity through a variety of interrelated mechanisms. Blood pressure is a function of cardiac output and peripheral vascular resistance (PVR) and obesity has actions that increase both components. Release of angiotensinogen from adipocytes stimulates the renin-angiotensin-aldosterone system (RAAS) leading to increased renal sodium resorption (and fluid retention), vasoconstriction and subsequent vascular hypertrophy. Activation of the sympathetic nervous system in obesity, possibly due to the actions of leptin, adiponectin, insulin and other adipocytokines, causes an increase in heart rate, increased peripheral vascular tone

and further activation of the RAAS (Dorresteijn, Visseren, & Spiering, 2012). Perivascular fat causes a mechanical increase in vascular stiffness, and PVR is further increased through increased blood viscosity (mediated by the prothrombotic changes of obesity). Endothelial dysfunction and consequent peripheral vasoconstriction contribute to hypertension through increasing PVR (as previously described). Finally, diets associated with obesity, such as those high in sodium and saturated fats, also contribute to the development of hypertension by potentiating the above mechanisms (Callaway et al., 2009; Dorresteijn et al., 2012; Van Gaal et al., 2006).

2.5.6. Visceral and ectopic adipose tissue

Individuals with the same degree of obesity have varying degrees of adipose-related complications. This is partly explained by differing body fat distributions. As discussed, visceral adiposity is reflected in waist circumference or waist-to-hip ratio measurements, which have been shown to predict metabolic syndrome, type 2 diabetes, stroke, myocardial infarction and subsequent cardiovascular mortality (Despres & Lemieux, 2006; Van Gaal et al., 2006; World Health Organization, 2000) (see also section 2.2 above). Visceral adipose tissue has physical and biochemical differences to subcutaneous adipose tissue. Compared with subcutaneous adipose tissue, visceral adipose tissue has increased cellularity, increased blood flow, higher cortisol and androgen receptors and is more prone to impaired suppression of adipocyte lipolysis (World Health Organization, 2000). It is also strongly associated with increased pro-inflammatory markers such as TNF-α, IL-6 and CRP, reduced adiponectin, increased endothelial dysfunction and insulin resistance. Consequently metabolic complications are increased in individuals that have greater visceral adiposity, compared with individuals that have predominantly subcutaneous adiposity (Despres & Lemieux, 2006; Van Gaal et al., 2006).

As excess energy is progressively stored in adipose tissue, cells undergo hypertrophy progressing to hyperplasia and eventually fat ‘spills over’ into ectopic storage which surrounds the skeletal muscle, liver, heart, blood vessels and kidney (Van Gaal et al., 2006). Ectopic fat, like visceral fat, carries a higher risk of metabolic disease. Storage of fat in ectopic sites can also impair organ function, either through metabolic or mechanical mechanisms. For example, myocardial fat accumulation may be directly cardiotoxic, liver fat has been directly associated with mortality risk and as previously mentioned, perivascular fat accumulation mechanically contributes to the increased vascular stiffness seen in obesity (Van Gaal et al., 2006). Excess visceral adipose tissue may also be, in effect, a type of ectopic fat. If subcutaneous adipose tissue is the body’s preferred energy storage site, then overwhelming this storage capacity would lead to fat being stored in the visceral compartment, possibly along with other ectopic sites. This then would provide some explanation as to why visceral and ectopic fat differ so greatly from subcutaneous fat in risk of adiposity-related complications (Despres & Lemieux, 2006).

As previously mentioned, genetic factors influence body composition. Under the influence of estrogen, women preferentially accumulate fat in a subcutaneous distribution, while men accumulate visceral fat (R. W. Taylor et al., 2010). In addition, the distribution of body fat differs between ethnicities along with differing percentage body-fat to muscle ratios. For example, not only do Asian and Indian populations have higher body-fat percentages for the same BMI as Europeans, they also have increased visceral adiposity. These ethnic differences may help to explain the higher rates of metabolic disease observed in Asian and Indian populations at lower BMI levels (McKeigue, Shah, & Marmot, 1991; Wang et al., 1994; WHO/IASO/IOTF, 2000) (see also section 4.3 below).

2.5.7. Obesity-related disease

The pathophysiological consequences of obesity described above explain the association between obesity and metabolic diseases such as metabolic syndrome, type 2 diabetes, hypertension, cardiovascular disease and non-alcoholic steatohepatitis (fatty liver). Obesity is also related to other diseases and morbidity through hormonal, mechanical or psychological mechanisms.

Excess adiposity has been shown to be associated with cancer, particularly hormone-dependent cancers of the reproductive tract and gastrointestinal cancers. The association between cancer and obesity is in part due to chronic inflammation and immune dysfunction as previously described, but other mechanisms are also involved. Gastrointestinal cancers such as cancer of the colon have been associated with insulin resistance but diets that pre-dispose to obesity such as high fat diets, may also play a role in their pathogenesis (Abate & Chandalia, 2003; Haslam & James, 2005; World Health Organization, 2000). In women, peripheral conversion of sex hormones by adipose tissue results in excess estrogen which is associated with postmenopausal breast and endometrial cancers. In premenopausal women, high levels of estrogen interrupt the hypothalamic, pituitary, ovarian axis resulting in irregular, commonly anovulatory menses and subfertility (Haslam & James, 2005).

Respiratory disease is more common in obesity. Accumulation of fat around the chest wall makes the work of breathing harder and predisposes to obstructive sleep apnoea and general hypoxaemia in a restrictive lung disease pattern (World Health Organization, 2000). In addition, inflammatory and immune changes in obesity are likely to contribute to the increased rates of asthma seen in obese individuals (Tilg & Moschen, 2006).

Obesity is associated with an increase in joint disease including osteoarthrosis and gout. Osteoarthrosis is thought to be caused by direct mechanical stress on joints in obesity, but may also be mediated by inflammatory processes. Gout is caused by hyperuricaemia, which is commonly elevated in individuals with metabolic syndrome, but is also associated with diets that pre-dispose to obesity.

Obese individuals have an increased chance of experiencing psychological disease, including depression, anxiety, social phobias and more rarely eating disorders (Haslam & James, 2005; World Health Organization, 2000). Although there is no direct evidence that obesity causes mood or anxiety disorders, consumption of foods high in carbohydrates may cause serotonin modulation within the brain with predisposed individuals learning to eat to increase serotonin levels (Wurtman & Wurtman, 1995). However, it is also likely that psychological disease can be reactive to social prejudice, bias or body shape dissatisfaction (Atlantis, Goldney, & Wittert, 2009; World Health Organization, 2000). The psychological effects of obesity are therefore likely to differ between cultures.

Obesity is also related to premature mortality. This association is difficult to study as there are many confounders of obesity including lower socioeconomic status, higher smoking rates etc. However, it seems that there is a progressive increase in mortality risk with increasing BMI (Engeland, Bjorge, Selmer, & Tverdal, 2003; Haslam & James, 2005; World Health Organization, 2000). The World Health Organization estimates at least 2.8 million people die each year as a result of excess adiposity, and 35.8 million (2.3%) of global disability-adjusted life years (DALYs)[2] are caused by overweight or obesity (World Health Organization, 2012a). In NZ in 1991 the healthcare costs attributed to obesity were estimated at $135 million or 2.5% of total health care costs; calculated for only six obesity-related conditions; diabetes, coronary heart disease, hypertension, gallbladder disease, postmenopausal breast cancer and colon cancer, and not accounting for the cost of premature mortality (Swinburn et al., 1997). Needless to say, obesity rates have increased since this time, with massive implications for both health systems and society.

2.6. Summary

Overweight and obesity are now considered a global epidemic, with escalating rates among developed and developing countries, and particularly among children and adolescents. The causes of obesity are poorly understood but multifactorial, and include biological, environmental and behavioural components. More recent discoveries of the importance of the *in-utero* fetal environment have suggested that fetal programming through epigenetic mechanisms may have a substantial impact on the risk of adult metabolic diseases including obesity. The pathophysiological changes seen with excess adiposity involve most organ systems and have a significant impact on general health and well-being. The metabolic changes associated with excess adiposity have considerable implications for pregnancy-related pathology, as discussed in Chapter 3.

[2] The disability-adjusted life year (DALY) is a measure of overall disease burden, expressed as the number of years lost due to ill-health, disability or early death (Wikipedia the free encyclopedia, 2012; World Health Organization, 2012b)

Chapter 3. | Overweight and obesity in pregnancy

3.1. Introduction

Previously a disease of older adults, overweight and obesity is becoming very common among women of childbearing age. Overweight and obesity in pregnancy is now widespread, and has serious implications for both fetus and mother. Complications throughout pregnancy are more prevalent in obese mothers in a 'dose dependent' fashion, and include subfertility, miscarriage, pre-eclampsia, gestational diabetes mellitus (GDM) as well as a higher risk of Caesarean section (CS) and postpartum haemorrhage (Catalano, 2007; Catalano & Ehrenberg, 2006; Heslehurst et al., 2008; Lashen, Fear, & Sturdee, 2004; Leddy, Power, & Schulkin, 2008; H. E. Robinson, O'Connell, Joseph, & McLeod, 2005). The infant of an obese mother is not only more often exposed to the above pregnancy complications, but also has a higher risk of adverse outcomes such as structural abnormalities, e.g. neural tube defects, an increased chance of macrosomia and a higher risk of stillbirth (Catalano, 2007; Chu et al., 2007; Clausen et al., 2005; Ehrenberg, Mercer, et al., 2004; Gunatilake & Perlow, 2011; Leddy et al., 2008). In addition, antenatal assessment and monitoring of infants of obese mothers is more challenging, both clinically and using ultrasound.

With increasing numbers of obese mothers, health systems need to be able to cope with a higher volume of high-risk pregnancies. This means increases in both inpatient and outpatient visits, higher numbers of investigations and interventions as well as the provision of specialist equipment (beds, wheelchairs, operating equipment etc.) to care for an increasing number of morbidly obese women. As a result, maternal obesity places a large financial and resource strain on health services (Chu et al., 2008; Heslehurst, Lang, Rankin, Wilkinson, & Summerbell, 2007).

3.2. Epidemiology of maternal obesity

Consistent with temporal increases in the general population, rates of overweight and obesity have also increased in obstetric populations (Alexandra et al., 2011; Ehrenberg, Dierker, Milluzzi, & Mercer, 2002; Heslehurst, Ells, et al., 2007; Kanagalingam, Forouhi, Greer, & Sattar, 2005; LaCoursiere, Bloebaum, Duncan, & Varner, 2005). Importantly, the degree of obesity also seems to be increasing with increasing numbers of class II and III obese women (McIntyre, Gibbons, Flenady, & Callaway, 2012; National Center for Health Statistics, 2011).

In NZ, national annual maternity statistics do not include BMI data. Unpublished national maternity data (also known as MAT) which includes information on approximately 84% of all NZ births since 2008, reveals that at the time of pregnancy booking, approximately 50% of women are overweight (BMI >25kg/m^2), and 22% obese (BMI ≥30kg/m^2) (PMMRC, 2012).

National Women's Health (NWH) in Auckland, NZ (a tertiary referral maternity hospital with approximately 7500 births/year), collects BMI, demographic and clinical data for all women delivering at the hospital. BMI data has been reliably collected since 2006 with BMI calculated for all women at the pregnancy booking visit from measured height and weight. NWH rates of overweight and obesity have remained stable at approximately 19% and 17% respectively since 2006, however the highest rates of overweight and obesity are observed in the youngest age groups (<25y 48%, Figure 3.1) (National Women's Health, 2012). As these younger women go on to have subsequent pregnancies, overall obesity rates at NWH may increase.

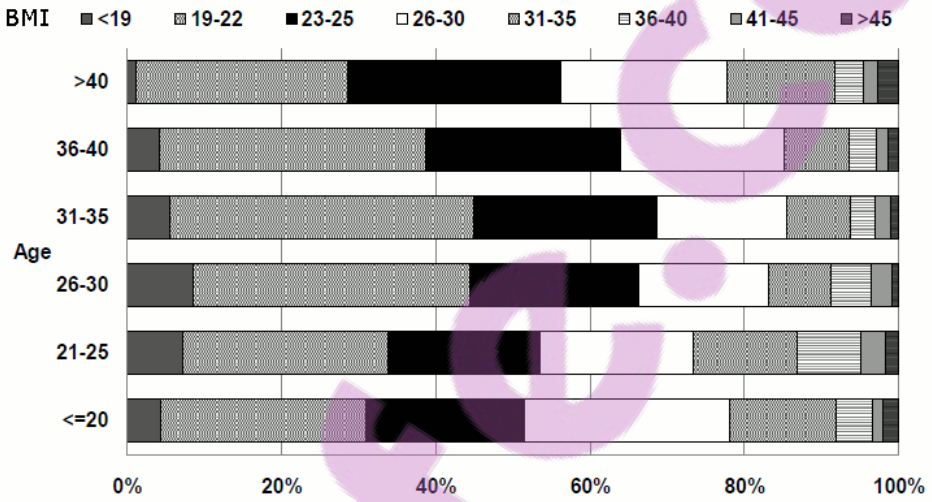


Figure 3.1. Distribution of BMI by maternal age at National Women's Health, 2011. Reproduced with permission, National Women's Health, 2012.

Just as in the general population, obesity rates in pregnancy differ by ethnicity (Centre for Maternal and Child Enquiries (CMACE), 2010; National Women's Health, 2012). At NWH the rates of obesity by ethnicity mirror those in the general population, with Māori and Pacific women most likely to be obese and Asian women least likely. Of concern, 60% of Pacific and 34% of Māori pregnant women are obese (BMI ≥30), compared with 11% of European, 10% of Indian and 5% of Asian pregnant women, Figure 3.2 (National Women's Health, 2012).

As with the general population, obesity in pregnancy has associations with other risk factors, such as low socioeconomic status and cigarette smoking, that contribute to adverse pregnancy outcomes (Centre for Maternal and Child Enquiries (CMACE), 2010; Heslehurst, Ells, et al., 2007). Studies that investigate pregnancy complications in obese women must therefore also adjust for these confounders (see also section 4.3 below).

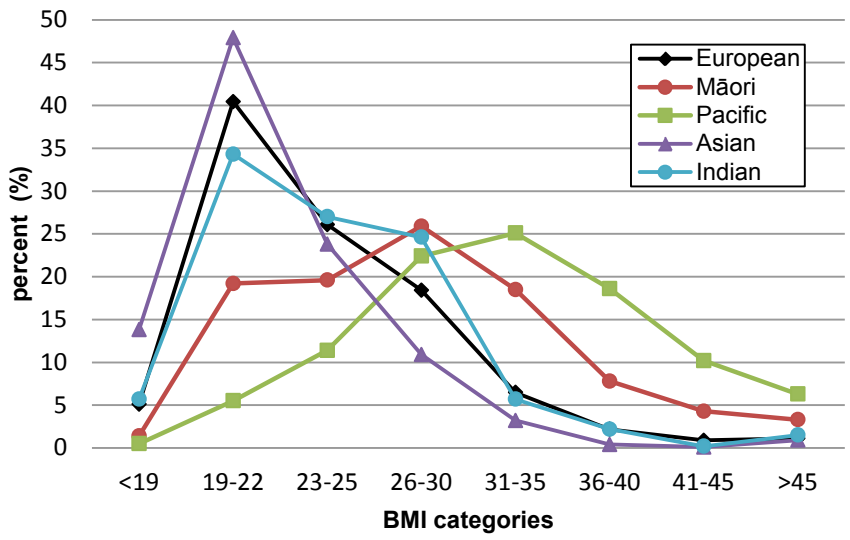


Figure 3.2.Distribution of BMI by major ethnicities at National Women's Health, 2011. Reproduced with permission National Women's Health, 2012.

3.3. The physiology of pregnancy and obesity

During pregnancy a vast number of physiological changes occur in the mother to accommodate the fetus. Some of the most important changes are metabolic and centre around the essential task of providing nutrition to the fetus and infant, but these changes also put substantial stress on maternal systems. Pregnancy complications such as pre-eclampsia or gestational diabetes occur when physiological stressors exceed the mother's ability to compensate (either through an increased load e.g. twin gestation, or a lower compensatory threshold e.g. pre-existing chronic hypertension or obesity) (Sibai, Dekker, & Kupferminc, 2005; D. Williams, 2003). Some have described pregnancy as a 'stress test for life', as for a short time women are exposed to a state resembling the metabolic syndrome. Women who are obese already have features of the metabolic syndrome and as a result have an impaired ability to compensate for the increased metabolic demands of pregnancy. Obese women therefore are more likely to manifest pregnancy complications such as hypertensive diseases of pregnancy and gestational diabetes. In addition, regardless of BMI, those who experience pregnancy complications have demonstrated a susceptibility to metabolic stress and consequently have a higher risk of developing later metabolic-related health conditions such as type 2 diabetes and hypertension (D. Williams, 2003).

3.3.1. Hormonal and metabolic changes

Physiological change starts early in pregnancy. Embryonic production of β-hCG is detectable in maternal serum as early as the eighth day after ovulation. Its function is to prevent the deterioration of the corpus luteum, thus preserving the production of progesterone which stabilises the endometrium (Feldt-Rasmussen & Mathiesen, 2011). Progesterone plays a dominant role throughout pregnancy by maintaining uterine quiescence (Challis et al., 2009;

Feldt-Rasmussen & Mathiesen, 2011), but as previously discussed progesterone also acts to promote hunger and food intake. Pregnancy is also a state of relative estrogen deficiency, resulting in an increase in appetite due to the absence of its anorectic effect (Asarian & Geary, 2006). These hormonal mechanisms enable storage of energy in preparation for the higher metabolic demands of late pregnancy and lactation (Augustine et al., 2008; Landau, 1983).

As excess energy is consumed and stored as fat, adipose signals to the central nervous system would normally limit further intake. In pregnancy this stimulus is over-ridden, and it has been found that pregnancy is a state of transient leptin resistance (Augustine et al., 2008). Leptin levels rise in early pregnancy before body weight increases, implying the rise is not initiated by increased adiposity. The origin of maternal hyperleptinamia is unknown, but placental production of leptin is likely to be a significant contributor. As with obesity, elevated leptin levels in pregnancy are associated with central leptin resistance, however it appears that the mechanism of leptin action on the central nervous system in pregnancy differs from that in obesity (Augustine et al., 2008). In pregnancy, leptin resistance induces a starvation-like signal to the mother despite adequate intake which encourages on going consumption of energy. This stimulus to eat occurs regardless of existing energy stores, meaning obese pregnant women have the same signals that encourage weight gain as normal weight pregnant women (Augustine et al., 2008). Of note, leptin may also have additional roles in pregnancy including regulation of fetal growth, with infant birthweight highly correlated with cord-blood leptin levels (Henson & Castracane, 2000, 2006) (see also section 3.4.1.1 below).

As pregnancy progresses and fetal nutrient demands increase, fasting blood glucose levels drop despite a significant increase in hepatic glucose production (Feldt-Rasmussen & Mathiesen, 2011). Steroid hormones from the feto-placental unit (particularly human placental lactogen, hPL) induce a progressive maternal insulin resistance, to which the maternal pancreas responds with increased insulin production. Basal insulin levels in late pregnancy can be up to two-fold greater than in the non-pregnant state. This insulin resistance results in a slight increase in post-prandial concentrations of glucose which is then available for fetal nutrition (Feldt-Rasmussen & Mathiesen, 2011). Additionally, lipid metabolism is altered in pregnancy, particularly late pregnancy, with an increase in circulating triglycerides, fatty acids, cholesterol and lipoproteins (secondary to insulin resistance). Both glucose and lipids are actively transported to the fetal circulation as fuel substrates (Catalano & Hauguel-De Mouzon, 2011; Feldt-Rasmussen & Mathiesen, 2011). As obesity is already a state of both insulin resistance and dyslipidaemia, the additional metabolic demands of pregnancy may lead to physiological decompensation manifesting as gestational diabetes (D. Williams, 2003). The presence of excess fuel substrates in obesity (both glucose and lipids) also predispose to increased fetal growth and macrosomia (Catalano & Hauguel-De Mouzon, 2011) (see also section 3.4.1.1 below).

Pregnancy is also characterised by a mild progressive inflammatory response which is likely required for immune tolerance of the fetus (Challis et al., 2009). Pro-inflammatory cytokines (particularly TNF-α and IL-6) are produced by the placenta (Feldt-Rasmussen & Mathiesen, 2011), and as previously discussed are also implicated in the development of insulin resistance, endothelial dysfunction and hypertension. Hypertensive disorders of pregnancy such as pre-eclampsia are characterised by an excessive inflammatory response in pregnancy (see also section 3.4.2 below).

3.3.2. Cardiovascular changes

In normal pregnancy, cardiovascular changes early in gestation lead to a significant increase in cardiac output as early as 5–6 weeks of gestation. Heart rate increases by 10–15bpm accompanied by an increase in blood volume and cardiac stroke volume, but compensated for by a systemic drop in peripheral vascular resistance through small vessel vasodilation. The overall effect is a small drop in blood pressure (BP) in early pregnancy (Weissgerber & Wolfe, 2006). Blood volume expansion in early pregnancy occurs primarily through an increase in plasma volume. The relative hypotension of the first trimester activates the RAAS, which along with progesterone acts to promote sodium and water retention, culminating in a 40–50% increase in plasma volume by term. BP continues to drop from early pregnancy to a nadir at 22–24 weeks of gestation followed by a progressive increase to term, Figure 3.3 (Grindheim, Estensen, Langesaeter, Rosseland, & Toska, 2012; M. J. A. Wilson et al., 1980).

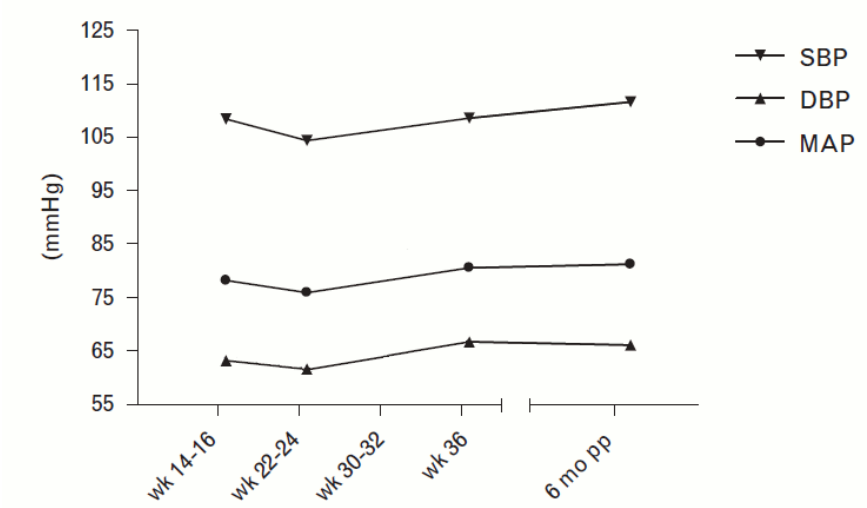


Figure 3.3. Changes in blood pressure during healthy pregnancy. SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure. Adapted from Journal of Hypertension, Grindheim et al. 2012. 30 (2) 342-350, with permission.

In obese women, the cardiovascular changes of pregnancy are dominated by hypertensive features. Not only do obese women enter pregnancy with a significantly higher BP than normal weight women (Grindheim et al., 2012), but obese women also have a limited ability to respond to the vasodilatory effects of early pregnancy. As previously mentioned, obesity is associated

with multiple mechanisms that predispose to hypertension (including oxidative stress, inflammation, endothelial dysfunction, increased sympathetic nervous system activity and RAAS stimulation), which is compounded in pregnancy by both progesterone effects on sodium and water retention as well as further stimulation of the RAAS (Dorresteijn et al., 2012; M. J. A. Wilson et al., 1980). Obesity-associated alterations in the normal cardiovascular changes of pregnancy contribute to the increased rates of hypertensive diseases of pregnancy that occur in overweight and obese mothers (see also section 3.4.2 below).

3.4. Specific pregnancy outcomes and obesity

Obesity has a detrimental impact on many pregnancy outcomes in a dose-dependent fashion. The following is a focussed review of the impact of obesity on three important and common outcomes of pregnancy that potentially have serious implications for mother and/or infant; infant birthweight, pre-eclampsia and CS. These outcomes are the focus of the publications in this thesis.

3.4.1. Infant birthweight and obesity

Maternal anthropometric measures are important contributors to birthweight. It is well established that increasing pre- or early- pregnancy maternal weight is positively correlated with increasing birthweight (Bukowski et al., 2008; Catalano, 2007; Gardosi, Mongelli, Wilcox, & Chang, 1995), but additionally, obesity is a well-recognised risk factor for excess fetal growth (macrosomia) (Catalano, 2007; Clausen et al., 2005; Ehrenberg, Mercer, et al., 2004; Henriksen, 2008; Owens et al., 2010). Obesity has also been considered protective for growth restriction with decreased rates of small for gestational age (SGA) infants in obese mothers when SGA has been defined by population birthweight standards (Kramer, 1987; McDonald, Han, Mulla, & Beyene, 2010; Thompson et al., 2001). More recent studies however have challenged this protective association, and obesity has been linked with increased rates of SGA infants when defined by customised birthweight standards (Gardosi, Clausson, & Francis, 2009; Gardosi & Francis, 2009b; McIntyre et al., 2012). (Further details on determinants of infant birthweight can be found in Chapter 5.)

3.4.1.1. Excess fetal growth and obesity

Accumulation of fetal adipose tissue does not occur until after 28 weeks of gestation, meaning excess fetal growth is predominantly a complication of late pregnancy (Yu & Upadhyay, 2004). Excess fetal growth is associated with an increased risk of both immediate and long term adverse outcomes for the infant, e.g. stillbirth, birth trauma, neonatal morbidity and mortality and adult disease (Catalano & Ehrenberg, 2006; Grassi & Giuliano, 2000; Henriksen, 2008), however there is no universally agreed definition of fetal growth excess.

Definition

Macrosomia is commonly defined using an absolute birthweight regardless of gestation, e.g. birthweight >4000g or >4500g, but the term 'macrosomia' is also commonly used synonymously with LGA, which is variably defined as a birthweight >90th population birthweight centile, >2 standard deviations of population birthweight and >90th customised birthweight centile (Cnattingius, Villamor, Lagerros, Wikstrom, & Granath, 2012; Grassi & Giuliano, 2000; Langer, 2000; Pasupathy et al., 2012). As normal fetal growth has many physiological contributors (please see Chapter 5), these definitions will inevitably include some normally grown infants however in general, infants that fall into these classifications are at increased risk of adverse outcomes. Regardless of definition, rates of macrosomia are increasing in many populations due to increasing rates of maternal overweight and obesity (Henriksen, 2008; Orskou, Kesmodel, Henriksen, & Secher, 2001). As excess adiposity is now common in modern obstetric populations, more macrosomic infants are now born to overweight and obese mothers than to diabetic mothers (Ehrenberg, Mercer, et al., 2004).

Aetiology

Macrosomia results from excess fuel substrates being provided to the infant for growth. Much of the research on aetiology and management of macrosomia has focussed on infants of diabetic mothers, with excess fetal growth associated with a chronic surplus of carbohydrate supplied to the fetus, resulting in fetal hyperinsulinaemia (Catalano & Hauguel-De Mouzon, 2011). Poor glycemic control in diabetic pregnancies has been found to predict neonatal macrosomia (Nold & Georgieff, 2004). The Pedersen hypothesis of macrosomia from the 1950's states "Maternal hyperglycaemia results in fetal hyperglycaemia and, hence, in hypertrophy of fetal islet tissue with insulin hypersecretion. This again means a greater fetal utilization of glucose. This phenomenon will explain several abnormal structure [sic] and changes found in the newborn" (Catalano & Hauguel-De Mouzon, 2011).

Insulin is an anabolic hormone and, consistent with the Pedersen hypothesis, fetal growth is positively associated with increasing fetal insulin levels (Langer, 2000). Insulin actions on fetal growth occur primarily through alterations in transcription of insulin-like growth factors (IGFs), particularly IGF-1 (Grassi & Giuliano, 2000). Cord serum IGF-1 levels are correlated with fetal growth with elevated levels associated with increased birthweight, (Ong et al., 2000; D. M. Wilson et al., 1982; Wiznitzer et al., 1998), but reduced levels are also found in growth restricted infants (Hills, English, & Chard, 1996; Woods, Camacho-Hubner, Savage, & Clark, 1996). Although IGF-1 is elevated in obese mothers, it (like insulin) does not cross the placenta and must be produced by the fetus in response to fetal insulin (Langer, 2000).

As may be expected, birthweight is also correlated with maternal glucose levels. The large prospective Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study in non-diabetic

women showed a linear relationship between increasing maternal glucose, higher umbilical cord C-peptide levels (a measure of fetal hyperinsulinaemia) and birthweight (HAPO Study Cooperative Research Group et al., 2008). As obese mothers without diabetes have higher daytime and nocturnal glucose compared to normal weight women (Harmon et al., 2011; Yogev et al., 2004), this association can begin to explain the association between maternal obesity and macrosomia. Increased birthweight however has also been observed in infants of obese mothers independent of maternal glucose levels (Ehrenberg, Mercer, et al., 2004; HAPO Study Cooperative Research Group, 2010).

As previously discussed, insulin resistance in late pregnancy results in increased lipolysis and increased circulating lipids (Catalano & Hauguel-De Mouzon, 2011). Obesity is associated with lipid abnormalities, and obese mothers have significantly higher triglyceride, VLDL cholesterol and lower HDL cholesterol in the third trimester compared to normal weight women (Ramsay et al., 2002). A strong independent association between maternal triglycerides and birthweight has been well established (Clausen et al., 2005; Di Cianni et al., 2005; Heerwagen, Miller, Barbour, & Friedman, 2010). Triglycerides are hydrolysed by placental lipoprotein lipase, and free fatty acids are transported to the fetus where, along with excess glucose, they are stored in fetal adipocytes, Figure 3.4.

Maternal triglycerides have been shown to be the strongest predictor of body fat in infants, although late pregnancy FFA, insulin and mean daytime glucose are also independently correlated with infant body fat (Harmon et al., 2011). Lipids are also likely to be a major contributor to fetal growth in gestational and type 2 diabetic pregnancies through these same mechanisms (Catalano & Hauguel-De Mouzon, 2011; E. Herrera & Ortega-Senovilla, 2010). Even after accounting for lipids and glucose, BMI still has an independent association with birthweight, meaning other as-yet unknown metabolic processes that affect fetal growth and

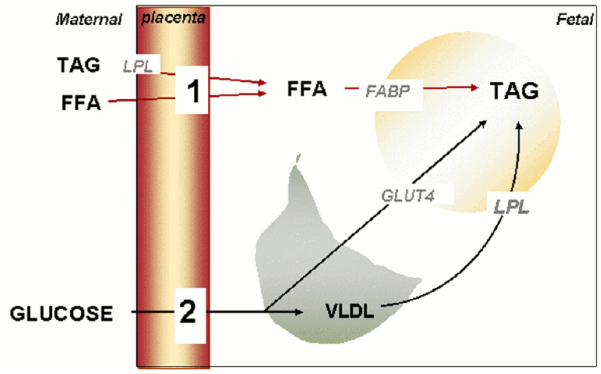


Figure 3.4. Energy substrates for lipogenesis in fetal adipocytes. TAG, triacylglycerol (triglyceride); LPL, lipoprotein lipase; FFA, free fatty acid; FABP, fatty acid binding protein; VLDL, very low density lipoprotein. Reprinted from American Journal of Obstetrics & Gynecology, 204 (6), Catalano et al., Is it time to revisit the Pedersen hypothesis in the face of the obesity epidemic?, 479-487, 2011., with permission from Elsevier.

postnatal outcomes are also likely. One of these factors may be leptin. Cord leptin levels have been positively correlated with increasing birthweight, and potentially fetal growth could be influenced by leptin-associated modulations of growth hormone production, or angiogenic processes during embryo implantation (Henson & Castracane, 2000, 2006). However as leptin levels are also related to fat mass, this may yet turn out to be an incidental finding (Langer, 2000).

Consequences

Increasing infant birthweight is associated with an increasing risk of birth complications including protracted labour, shoulder dystocia, perinatal asphyxia, birth injuries and an increased risk of CS (Boulet, Salihu, & Alexander, 2004; Grassi & Giuliano, 2000; Henriksen, 2008). Infants of diabetic mothers are at even greater risk, probably due to increased fetal adiposity (Grassi & Giuliano, 2000). Macrosomia due to intrauterine over-nutrition (rather than genetic factors) preferentially increases fat mass over lean body mass (Catalano & Hauguel-De Mouzon, 2011; Catalano, Thomas, Huston-Presley, & Amini, 2003). Infants of both diabetic and obese women have a greater fat mass when compared to infants of the same birthweight from lean, non-diabetic mothers (Catalano, 2007; Catalano et al., 2003; Sewell, Huston-Presley, Super, & Catalano, 2006). In addition, the physiologic and metabolic adaptations associated with chronic intrauterine hyperinsulinaemia have specific risks for the fetus, particularly in late gestation and in the newborn period, Figure 3.5.

As previously discussed, the long term implications of macrosomia relate to epigenetic fetal programming and increased risk of metabolic syndrome (Boney et al., 2005; Catalano & Ehrenberg, 2006; Catalano & Hauguel-De Mouzon, 2011; Heerwagen et al., 2010; Hermann, Dallas, Haskell, & Roghair, 2010) (see also section 2.4.3 above). Women who were themselves born LGA have an increased risk of being overweight or obese at the time of childbearing, but also have an increased risk of having an LGA child independent of their pre-pregnancy BMI (Cnattingius et al., 2012). The risk of an LGA infant for a women herself born LGA increases with increasing maternal BMI; women born LGA with a normal BMI (≤24.9kg/m^2) have a 3.5-fold increase in odds, while women born LGA who are obese class II or more (BMI ≥35kg/m^2) have a greater than 14-fold increase in odds compared with women born with a normal birthweight who have a normal BMI (Cnattingius et al., 2012). This then is a vicious cycle of maternal obesity leading to fetal overgrowth leading to childhood, adult and maternal obesity, Figure 3.6 (Cnattingius et al., 2012; Gluckman & Hanson, 2008).

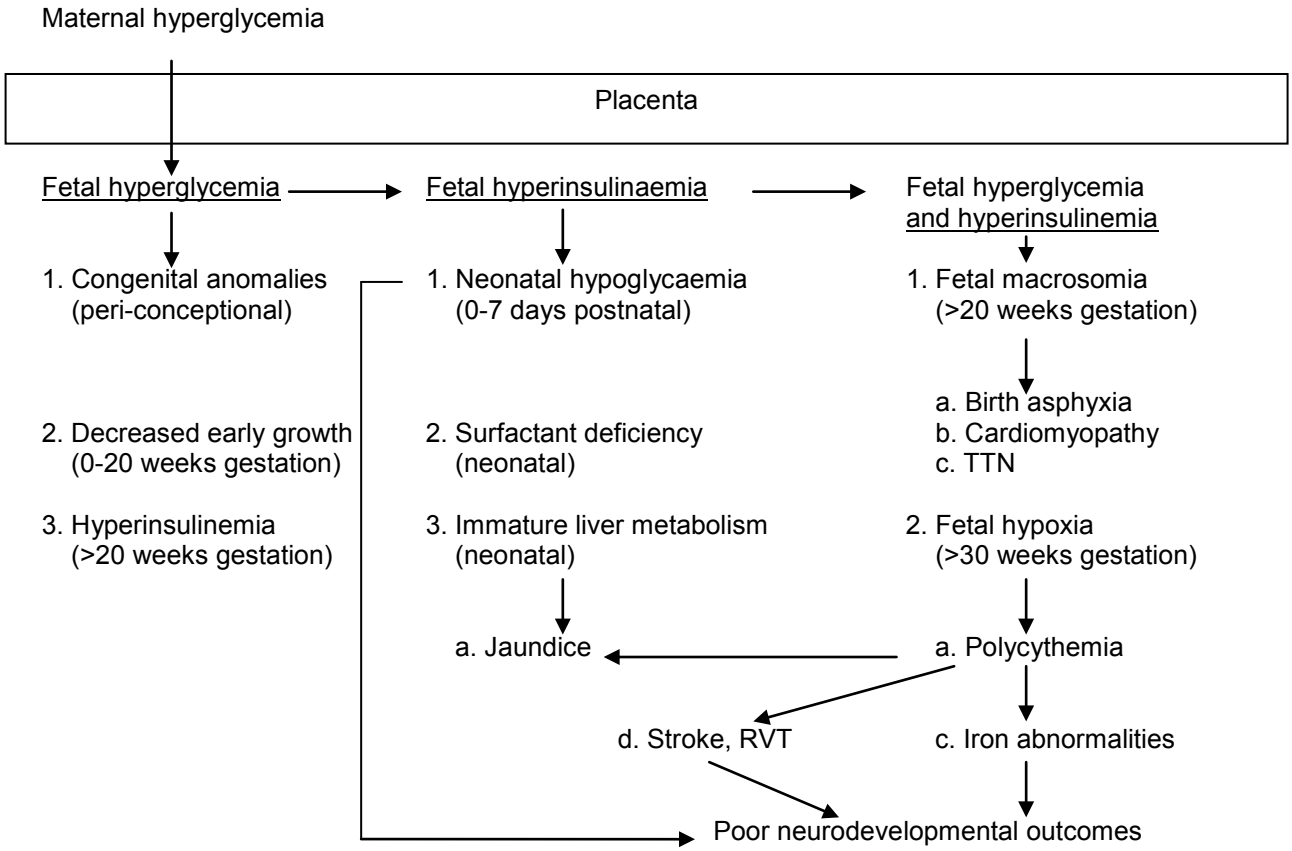


Figure 3.5. The fetal and neonatal events attributable to fetal hyperglycemia and hyperinsulinemia. TTN, transient tachypnoea of the newborn; RVT, renal vein thrombosis. Reprinted from Pediatric Clinics of North America, 51, Nold et al., Infants of diabetic mothers, 619-37, 2004, with permission from Elsevier.

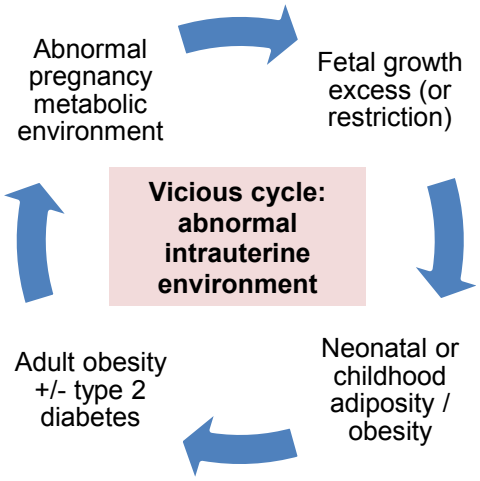


Figure 3.6. Vicious cycle resulting from an abnormal intrauterine metabolic environment. Fetal growth excess (or restriction) programmes the fetus for childhood and adult obesity and/or type 2 diabetes, perpetuating this cycle.

Management

Prevention strategies for macrosomia involve weight-loss prior to pregnancy, minimisation of gestational weight gain (GWG) in obese women and tight blood sugar control in diabetic women (Crowther et al., 2005; J. Smith et al., 2009; Thangaratinam et al., 2012) (see also section 3.4.4 below). Currently there are no interventions that reliably alter outcomes for macrosomic infants, partially due to the inaccuracies of antenatal diagnosis of macrosomia by ultrasound (Australasian Society for Ultrasound in Medicine, 2001-2007b). It has been estimated that in infants with an ultrasound estimated fetal weight >4.5kg, to prevent one permanent brachial plexus injury 443 CS would be needed in diabetic women, with that number increasing to 3695 CS for non-diabetic women (Rouse, Owen, Goldenberg, & Cliver, 1996). More recently a randomised controlled trial has suggested that elective induction of labour for suspected macrosomia may reduce neonatal trauma without increasing CS risk (Boulvain, Senat, Rozenberg, & Irion, 2012), however a prior systematic review did not find any difference in neonatal or maternal outcomes with this same intervention (Irion & Boulvain, 1998). As such elective induction of labour cannot be currently recommended.

3.4.1.2. Fetal growth restriction and obesity

Fetal growth restriction (FGR) is associated with a substantially increased risk of perinatal morbidity and mortality as well as the consequences of fetal programming as previously described (Alberry & Soothill, 2007; Yu & Upadhyay, 2004) (see also section 2.4.3 above). In NZ, one in every 90 babies is stillborn or dies in neonatal life, and approximately 50% of these deaths occur in infants who are SGA (PMMRC, 2012). More recently, obese women have been shown to have increased rates of SGA infants, when SGA is defined by a customised birthweight standard (Gardosi & Francis, 2009b; McIntyre et al., 2012; Rajasingam, Seed, Briley, Shennan, & Poston, 2009). This association between excess adiposity and impaired fetal growth is interesting as it may help to explain the increased rates of perinatal death observed in obese mothers (Gardosi et al., 2009).

Definition

FGR can be considered the failure of the fetus to reach its growth potential, primarily due to chronic undernutrition from uteroplacental insufficiency (Kramer, 1987). As with macrosomia, there is no universal definition to identify FGR. Commonly, SGA is used as a surrogate marker of FGR, where definitions vary but include a birthweight <10th, <5th and <3rd population birthweight centile, <2 standard deviations of population or estimated (ultrasound-based) fetal weight, and <10th customised birthweight centile, all adjusted for gestational age (Gardosi, Mongelli, Wilcox, et al., 1995; Lindqvist & Molin, 2005; P. Owen, Ogah, Bachmann, & Khan, 2003; Surkan, Stephansson, Dickman, & Cnattingius, 2004; Thompson et al., 2001). Infants who are SGA are more likely to be growth restricted than non-SGA infants, but as with LGA, inevitably

some infants will be misclassified. Further details on determinants of fetal growth and birthweight can be found in Chapter 5.

Currently the most widely used definition of SGA is <10th population birthweight centile for gestational age (Alberry & Soothill, 2007; Thompson et al., 2001; J. Zhang, Merialdi, Platt, & Kramer, 2010). Studies investigating SGA risk factors that use population birthweight references show that underweight women have an increased risk of SGA, while excess adiposity is protective of SGA (Cnattingius, Bergstrom, Lipworth, & Kramer, 1998; Kramer, Platt, Yang, McNamara, & Usher, 1999; Nohr et al., 2008; Thompson et al., 2001). Population birthweight references are derived from an average birthweight for gestational age, and do not take account of maternal characteristics (or other factors) that also contribute to infant birthweight. Multivariable regression models of birthweight have consistently shown independent associations between increasing maternal height and weight, and increasing birthweight (Bukowski et al., 2008; Gardosi & Francis, 2009b; Gardosi, Mongelli, Wilcox, et al., 1995; Pang, Leung, Sahota, Lau, & Chang, 2000; Sahota, Kagan, Lau, Leung, & Nicolaides, 2008; X. Zhang, Cnattingius, Platt, Joseph, & Kramer, 2007). As a result, population birthweight references may underestimate SGA rates in tall or heavy women, and overestimate SGA rates in short or light women. Customised birthweight standards not only adjust for maternal height and weight, but also account for other influences on birthweight such as parity, ethnicity, infant sex, smoking, hypertensive disease and diabetes (Gardosi, 2004; Gardosi, Chang, Kalyan, Sahota, & Symonds, 1992).

The association between obesity and FGR

When expected birthweight is adjusted for maternal characteristics, an association between obesity and impaired fetal growth is revealed. Gardosi and colleagues developed a multivariable regression model for customised birthweight in a US population and included high BMI (defined as >90th centile of BMI in their population, i.e. >31.7kg/m^2) as an independent variable in addition to height and weight. (Gardosi & Francis, 2009b). They found that high BMI was independently associated with a 63g decrease in birthweight at term. (To give this value context antepartum haemorrhage, which has a well-established association with FGR (McCormack, Doherty, Magann, Hutchinson, & Newnham, 2008), had a 41g decrease in birthweight at term). This negative association (after already adjusting for height and weight) suggests that fetal growth may be impaired in obese women.

In the previous section of this thesis, the association between maternal obesity, macrosomia and increased perinatal morbidity has been discussed. It can be argued that adjusting for increasing maternal weight may inappropriately normalise excess fetal growth that may be pathological. In addition Hutcheon, J Zhang and X Zhang et al. have questioned the appropriateness and value of adjusting for maternal characteristics such as height and weight in birthweight references

(Hutcheon, Zhang, Cnattingius, Kramer, & Platt, 2008; J. Zhang et al., 2010; X. Zhang, Platt, Cnattingius, Joseph, & Kramer, 2007). It is important therefore to look at infant outcomes. To do this, Gardosi and colleagues assessed the value of adjusting for maternal characteristics in birthweight customisation by investigating perinatal death rates in subgroups of women (Gardosi et al., 2009). They first compared rates of perinatal death between infants defined as SGA by customised (SGAcust) and population (SGApop) birthweight centiles, in a large European population of women with normal BMIs but differing heights and weights, Figure 3.7. As the BMI range was restricted to 20-24kg/m^2, increasing maternal weight was associated with increasing maternal height. Rates of SGAcust did not differ between maternal weight groups (as expected), however rates of SGApop varied substantially from 17.8% in the lower weight group to 7.9% in the upper weight group, Figure 3.7. Despite the differing rates of SGApop, there were no differences in risk of perinatal death between any groups, and the authors suggest this reflects an over-diagnosis of SGApop among smaller women, and under-diagnosis SGApop among larger women.

In this same study, Gardosi and colleagues also investigated rates of SGA and perinatal death between traditional WHO BMI groups. They observed a dramatic decrease in SGApop rates from 18% among underweight women to 8% among obese women, while rates of SGAcust were increased among overweight and obese women, Figure 3.8. Perinatal death rates also increased with increasing BMI, with the perinatal mortality rate by BMI correlated with SGAcust rates, but not with SGApop rates, Figure 3.8. This observation again suggests that SGApop is over-diagnosed among underweight, and under-diagnosed among overweight and obese women. Importantly, as no adjustment for confounding factors of perinatal death was performed, the argument of Gardosi and colleagues relies on the assumption that the differences in perinatal mortality rates by BMI (or weight category) reflect differences in SGA rates alone, which has not yet been demonstrated. As up to 50% of perinatal deaths are among infants who are SGA (Gardosi, Kady, McGeown, Francis, & Tonks, 2005; PMMRC, 2012) this assumption is not unreasonable but results must be interpreted cautiously.

Higher rates of SGAcust among obese mothers have been previously reported (Rajasingam et al., 2009), however only one previous study has formally investigated risk factors for SGAcust using multivariable analysis, but in a healthy nulliparous cohort (L.M.E. McCowan et al., 2010). This prospective study found women with SGA infants and hypertensive disease had a higher BMI than women with SGA infants and no associated hypertensive disease; although on multivariable analysis BMI was not associated with risk of SGA. A single study that included a limited multivariable analysis of SGAcust by maternal BMI in a general obstetric population found an increasing risk of SGAcust with increasing BMI (McIntyre et al., 2012). They also observed the well-established protective effect of increasing BMI on SGApop. This study was only able to

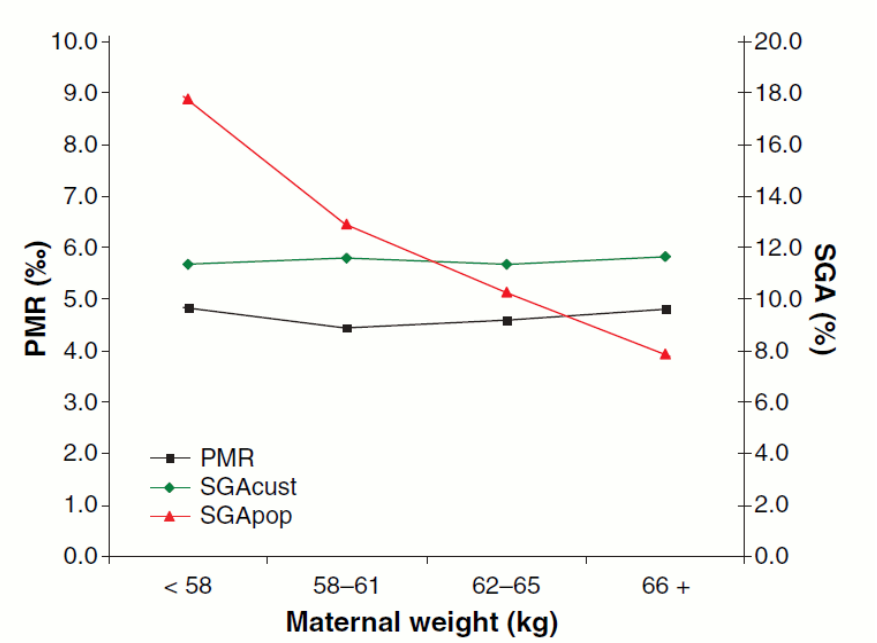


Figure 3.7. Perinatal mortality rate (PMR) and small for gestational age (SGA) rate by customised (SGAcust) and population-based centiles (SGApop), according to maternal weights within normal body mass index (BMI 20–24.9). *t*-test fordifference of slopes: PMR versus SGAcust: *P*=0.743; PMR versus SGApop: *P*<0.001. Reproduced from Gardosi et al., BJOG (2009), The value of customised centiles in assessing perinatal mortality risk associated with parity and maternal size, 116 (10) 1356-1363. DOI: 10.1111/j.1471-0528.2009.02245.x with permission.

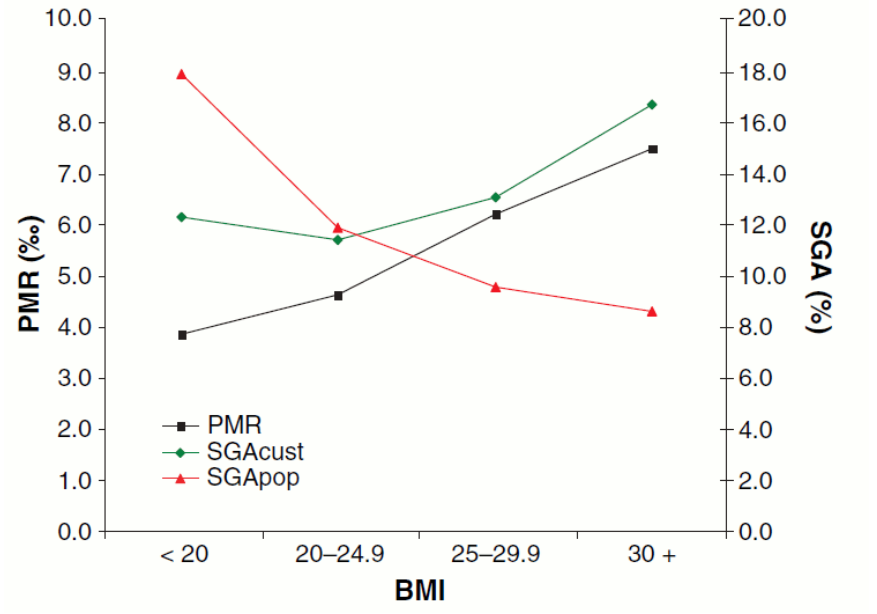


Figure 3.8. Perinatal mortality rate (PMR) and small for gestational age (SGA) rate by customised (SGAcust) and population-based centiles (SGApop), according to maternal body mass index (BMI). *t*-test for difference of slopes: PMR versus SGAcust: *P*=0.753; PMR versus SGApop: *P*=0.007. Reproduced from Gardosi et al., BJOG (2009), The value of customised centiles in assessing perinatal mortality risk associated with parity and maternal size, 116 (10) 1356-1363. DOI: 10.1111/j.1471-0528.2009.02245.x with permission.

include a restricted number of confounding variables (maternal age, parity, insurance status, smoking, ethnicity and year of birth).

Aetiology

Given the well established association between obesity and excess fetal growth, at first an association between obesity and FGR can seem counterintuitive. However obesity has many mechanisms which could also impair fetal growth. Alterations or reductions in fetal growth occur in the presence of inadequate placental function restricting fetal substrate supply and causing chronic relative fetal hypoxia (Halliday, 2009; McMillen et al., 2001). Although FGR commonly presents late in pregnancy, placental dysfunction begins early in pregnancy with impaired trophoblastic invasion of the maternal spiral arteries, and inadequate conversion of maternal spiral arteries into wide non-muscular channels for facilitating transfer of nutrients (Kaufmann, Black, & Huppertz, 2003; Zhong, Tuuli, & Odibo, 2010). This same pathophysiology is also shared with pre-eclampsia, and interestingly the association between obesity and hypertensive disorders of pregnancy is well established (Callaway et al., 2009). Inflammation, oxidative stress, vasoconstriction, hypertension and impaired immunity are all associated with placental dysfunction, and are all potential contributors to obesity-related FGR (Ness & Sibai, 2006; Redman & Sargent, 2003). An outline of the shared pathophysiology of placental dysfunction in FGR and pre-eclampsia follows in section 3.4.2 below.

Consequences

As previously mentioned FGR is associated with an increased risk of perinatal death as well as increased perinatal morbidity. Growth restricted newborns are at increased risk of complications such as prematurity (both iatrogenic and spontaneous), birth asphyxia, cerebral palsy, hypoglycaemia, hypocalcaemia, hypothermia, polycythaemia, and sepsis (Halliday, 2009; Yu & Upadhyay, 2004). Children who are born growth restricted are more likely to have neuro-developmental delay, lower IQ, and have higher rates of childhood obesity and markers of metabolic disease (Boers et al., 2007; Boney et al., 2005; J. A. Low et al., 1992; van Wassenaer, 2005). These complications arise from the fetal adaptations that are required for the fetus to tolerate a hostile intrauterine environment (McMillen et al., 2001). This same intrauterine environment is also responsible for fetal programming of adult metabolic disease (Barker, 2004), which feeds into the same vicious cycle as macrosomia, Figure 3.6 (Gluckman & Hanson, 2008). Women who were born SGA are not only at increased risk of adult obesity, they have been shown to be at increased risk of having both SGA (Jaquet et al., 2005), and LGA infants (Cnattingius et al., 2012), presumably due to a predisposition to an abnormal intrauterine metabolic environment. In addition, women who have an SGA child are at increased risk of later cardiovascular disease which is independent of BMI, which may also relate to metabolic factors (Ness & Sibai, 2006; G. C. Smith, Pell, & Walsh, 2001; G. D. Smith, Harding, & Rosato, 2000).

Management

As with macrosomia, FGR is predominantly a disease of later pregnancy, when a dysfunctional placenta cannot keep up with the increasing metabolic demands of the growing fetus. Importantly, over 70% of SGA infants are delivered at term, which is partly due to the difficulties surrounding the antenatal diagnosis of SGA (Boers et al., 2010; Clausson, Cnattingius, & Axelsson, 1998; K.M. Groom, Poppe, North, & al., 2007; Lindqvist & Molin, 2005; L.M.E. McCowan et al., 2010).

The only management known to reduce the risk of FGR occurs before FGR can be diagnosed. Early prophylactic intervention with low-dose aspirin before placentation is complete may improve trophoblast invasion and remodelling of the maternal spiral arteries, however the overall reduction in risk is only in the order of 10% (RR 0.90, 95%CI 0.83–0.98) (Duley, Henderson-Smart, Meher, & King, 2007). In high risk pregnancies the reduction in risk is greater (56%; RR 0.44, 95% CI 0.30–0.65), but only if aspirin is started prior to 16 weeks of gestation (Bujold et al., 2010), providing indirect evidence that the mechanism of aspirin action relates to the improvement of placentation. As a result, women at higher risk of FGR (e.g. women with chronic hypertension, renal disease, previous FGR etc.) will derive greater benefit from this intervention than low risk women (see also section 5.2.2 below).

Management of established FGR centres around identification and timely delivery. Once FGR is identified, no therapies have yet been shown to increase fetal growth in pregnancy. Timely delivery of preterm growth restricted infants is a delicate balance between early delivery with neonatal consequences of prematurity (including neonatal death) and the risk of stillbirth (Grit Study Group, 2003). Antenatal identification of SGA however can reduce the risk of perinatal adverse outcomes such as birth asphyxia and stillbirth (Lindqvist & Molin, 2005) through increased fetal monitoring and iatrogenic delivery (induction of labour or elective CS). Currently, fewer than 50% of SGA infants are detected prior to birth (Gardosi & Francis, 1999; Hepburn & Rosenberg, 1986; Lindqvist & Molin, 2005; Roex, Nikpoor, van Eerd, Hodyl, & Dekker, 2012) and in obese women this detection rate is even less (M. Williams, Southam, & Gardosi, 2010). A better understanding of risk factors for fetal growth restriction may allow improved antenatal identification of at-risk women and pregnancies, leading to increased surveillance and improved perinatal outcomes.

3.4.1.3. Summary

Obesity has a paradoxical relationship with birthweight, with a well-established association with increased rates of macrosomia, but also a likely association with increased rates of SGA. Both macrosomia and FGR result from an abnormal intrauterine environment which results in abnormal fetal epigenetic programming. This leads to an increased chance of longterm health consequences and a vicious cycle of complications propagating between generations.

Antenatal identification and iatrogenic delivery of suspected macrosomia may improve neonatal outcomes however accurate antenatal detection is poor and data are limited. Although antenatal identification of SGA is also currently poor, it has been shown to reduce perinatal morbidity and stillbirth through increased surveillance and timely delivery.

There are many factors other than obesity that contribute to an infant's birthweight, both physiological and pathological, and a review of these factors can be found in Chapter 5.

3.4.2. Pre-eclampsia and obesity

Pre-eclampsia is a common multisystem disease of pregnancy affecting approximately 2% of all pregnancies and up to 7% of nulliparous women (Duckitt & Harrington, 2005; Sibai et al., 2005). Obesity is a well-established risk factor for pre-eclampsia with increasing risk associated with increasing adiposity in a dose dependent fashion (Bodnar, Catov, Klebanoff, Ness, & Roberts, 2007; Bodnar, Ness, Markovic, & Roberts, 2005; Callaway et al., 2009; Mbah et al., 2010; O'Brien et al., 2003).

Pre-eclampsia is characterised by new-onset gestational hypertension (occurring after 20 weeks of pregnancy) with proteinuria or other multisystem complications such as renal impairment, liver dysfunction, neurological or haematological disturbances (Brown, Lindheimer, de Swiet, Van Assche, & Moutquin, 2001; S. A. Lowe et al., 2009). Eclampsia, the development of seizures on a background of pre-eclampsia, is rare in developed countries (approximately 0.5:1000 births) due to early identification of pre-eclampsia, but is much more common in developing countries (approximately 6:1000 births) (Khan, Wojdyla, Say, Gülmezoglu, & Van Look, 2006; Moodley & Daya, 1994; The Magpie Trial Collaborative Group, 2002). In both developed and developing countries, pre-eclampsia and eclampsia are major causes of maternal morbidity and mortality (Khan et al., 2006; The Magpie Trial Collaborative Group, 2002). The fetal consequences of pre-eclampsia include FGR, preterm birth, birth asphyxia, increased neonatal admission and perinatal death along with the long term epigenetic programming consequences of preterm birth and FGR (Ahmad & Samuelsen, 2012; Habli, Levine, Qian, & Sibai, 2007; Sibai et al., 2005). As with FGR, women who develop pre-eclampsia are also at increased risk of cardiovascular disease later in life (Mongraw-Chaffin, Cirillo, & Cohn, 2010; Ramsay, Stewart, Greer, & Sattar, 2003; G. C. Smith et al., 2001; B. J. Wilson et al., 2003).

Pre-eclampsia is becoming increasingly common. Age-adjusted incidences of both gestational hypertension and pre-eclampsia have increased in the USA (Figure 3.9) which is likely due to an increase in underlying risk factors such as obesity, diabetes, and chronic hypertension (LaCoursiere et al., 2005; Wallis, Saftlas, Hsia, & Atrash, 2008). On-going increases in rates of obesity in the general population, particularly childhood and young adult obesity, is a likely indicator of continuing increases in pre-eclampsia prevalence in future obstetric populations.

Aetiology

It is likely that the clinical entity of pre-eclampsia is the final common phenotypic pathway resulting from multiple aetiologies. It is clear that a placenta must be present for pre-eclampsia to develop, with the only treatment of pre-eclampsia being removal of the placenta (and delivery of the fetus). Pre-eclampsia therefore is caused by the placenta or the maternal response to the placenta, or more likely a combination of both (Sibai et al., 2005). It is thought that the key abnormalities underlying the pathophysiology of pre-eclampsia are endothelial dysfunction and defective placentation.

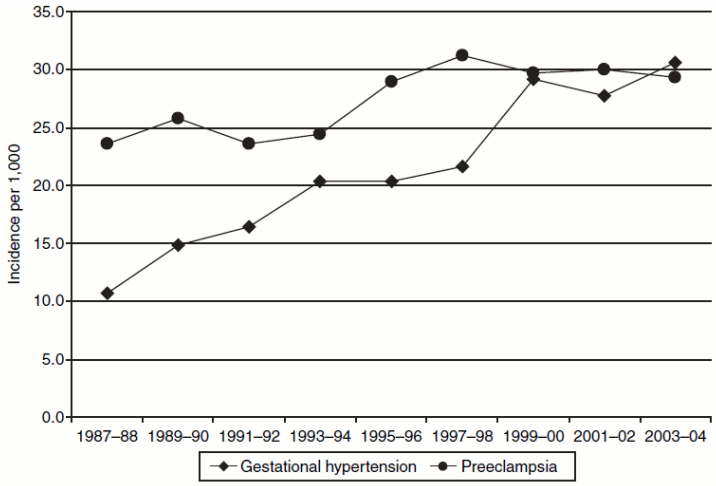


Figure 3.9. Age-adjusted incidence per 1000 deliveries for women with gestational hypertension or pre-eclampsia for 2-year periods, 1987–2004. Reprinted by permission from Macmillan Publishers Ltd: American Journal of Hypertension (2008), Wallis et al. Secular trends in the rates of preeclampsia, eclampsia, and gestational hypertension, United States, 1987-2004. 21 (5) 521-6.

Endothelial dysfunction

Endothelial dysfunction is a hallmark of pre-eclampsia involving both the maternal and fetal circulations. The most common manifestations of pre-eclampsia, namely hypertension and proteinuria, result from systemic maternal endothelial dysfunction (Callaway et al., 2009; Sibai et al., 2005; Solomon & Seely, 2006). The role of the endothelium in the pathogenesis of pre-eclampsia is supported by the observation that disorders predisposing to pre-eclampsia often involve varying degrees of endothelial dysfunction; e.g. maternal hypertension, renal disease, antiphospholipid syndrome and systemic lupus erythematosus. Additionally, higher rates of pre-eclampsia are observed in women with a family history of hypertension, coronary heart disease or cerebrovascular disease (Duckitt & Harrington, 2005; Ness & Sibai, 2006; North et al., 2011). Further, an increased risk of pre-eclampsia in women with infections in pregnancy (such as urinary tract, chlamydial and cytomegalovirus infections) is also consistent with systemic endothelial dysfunction from a generalised inflammatory process leading to pre-eclampsia (Callaway et al., 2009; Sibai et al., 2005).

Endothelial dysfunction occurs in the presence of endothelial damage. The normal response of the endothelium to damage is endothelial cell activation and a release of bioactive substances that influence vessel tone, remodelling and ultimately repair. However, in a chronic pathological process such as pre-eclampsia these substances can lead to a vicious cycle of vasospasm, thrombosis and increased vascular permeability that continues until all stimulating factors are removed (R. N. Taylor et al., 2009).

One of the precipitants of endothelial dysfunction in pre-eclampsia is likely placental debris. In normal pregnancy, the syncytiotrophoblast (a single multinucleated epithelial cell that covers the entire placental surface) normally undergoes continual renewal of aged or damaged material by extruding a membrane-enclosed multinucleated structure called a syncytial knot. This apoptosis-like process likely facilitates maternal immune tolerance of placental/ fetal antigens, Figure 3.10. In pre-eclampsia however, syncytial knots are increased due to increased shedding of aponecrotic or necrotic trophoblast debris (as a result of placental ischaemia/necrosis). This abnormal trophoblast debris activates endothelial cells and interferes with maternal immune tolerance, leading to increased secretion of pro-inflammatory cytokines, up-regulation of adhesion molecules and formation of neutrophil extracellular nets (NETs; fibrous extracellular DNA-containing lattices that may impair blood-flow at the materno-placental interface) (Askelund & Chamley, 2011; Pantham, Askelund, & Chamley, 2011). Placental hypoperfusion therefore is a vicious cycle of increased trophoblast debris causing endothelial dysfunction leading to further impairment of placental perfusion, Figure 3.10.

As previously mentioned, damage to, and activation of endothelial cells, can be initiated by many substances other than circulating placental debris including immune complexes, pro-inflammatory mediators, ROS and abnormal lipids (Bodnar, Ness, Harger, & Roberts, 2005; Callaway et al., 2009; R. N. Taylor et al., 2009; Wiznitzer et al., 2009; Zavalza-Gomez, 2011) (see section 2.5.3 above). As these substances are present in all pregnancies, the difference between normal pregnancy and pre-eclampsia may be an excess of placental debris (e.g. multiple gestation, poor placental perfusion), an exaggerated maternal response to the presence of the trophoblast (e.g. genetic or immune factors), or a lowered compensatory threshold for pregnancy due to pre-existing disorders including obesity (Sibai et al., 2005).

Placental dysfunction

Pre-eclampsia, particularly early-onset pre-eclampsia, can be characterised in the placenta by abnormal shallow implantation of fetal trophoblast and impaired transformation of the maternal spiral arteries from muscular high-resistance vessels to wide, non-muscular low resistance vessels (Ness & Sibai, 2006; Sibai et al., 2005). As a result, the placenta becomes hypoperfused leading to varying degrees of placental ischaemia and necrosis followed by inflammation and oxidative stress. This placental hypoperfusion also restricts nutrient and oxygen supply to the

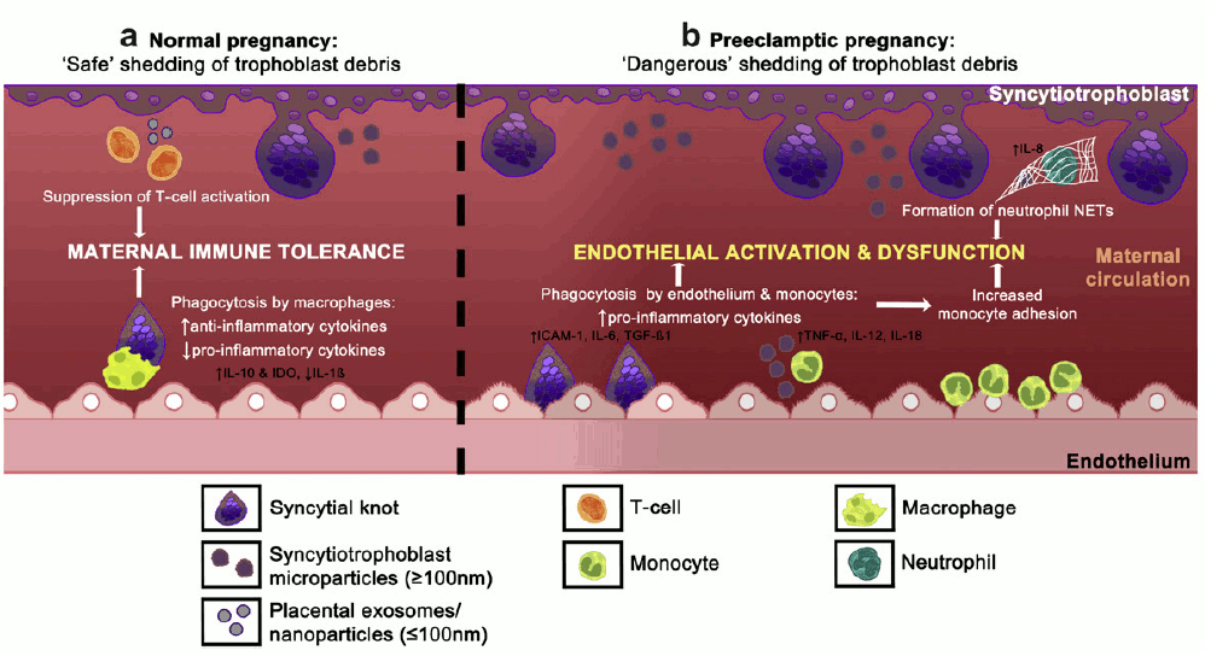


Figure 3.10. Schematic representation of the known immune and vascular effects of trophoblastic debris. IL, interleukin; IDO, indoleamine dioxygenase (an immunosuppressive enzyme); ICAM, intercellular adhesion molecule; TGF, transforming growth factor (a pro-inflammatory cytokine); TNF, tumour necrosis factor; NETs, neutrophil extracellular traps. Reprinted from Placenta, 32 (10) Pantham et al., Trophoblast deportation part II: a review of the maternal consequences of trophoblast deportation, 724-31, 2011, with permission from Elsevier.

growing fetus, and leads in some cases to FGR. The exact cause of incomplete trophoblastic invasion into the maternal uterine vasculature is unclear, however it is likely to be related to immune maladaptations (maternal and/or paternal in origin), maternal endothelial dysfunction and alterations in placental angiogenic factors (Callaway et al., 2009; Sibai et al., 2005).

As demonstrated by Figure 3.10, maternal immune tolerance of the placenta is important for normal pregnancy. This tolerance may be impaired in the presence of increased placental debris as previously discussed, but immune maladaptations also occur with maternal disorders such as insulin resistance, dyslipidaemia and obesity. In addition, some fetal antigens may be particularly immunogenic (i.e. a maternal alloimmune reaction to the fetal allograft), or immune dysfunction may result from a maternal genetic pre-disposition. Well established associations between pre-eclampsia and limited sperm exposure, primipaternity (particularly primiparity), and pregnancies with donor gametes reinforce the importance of immunity in the pathogenesis of pre-eclampsia (Callaway et al., 2009; Duckitt & Harrington, 2005; Kho et al., 2009; North et al., 2011; Sibai et al., 2005). This is further evidenced by markedly reduced rates of pre-eclampsia among immunosuppressed women, e.g. women with untreated HIV (Wimalasundera et al., 2002).

Trophoblast invasion of the fetal allograft into the uterus is normally accompanied by a maternal immune response in early pregnancy, particularly involving maternal natural killer (NK) cells. These NK cells function through direct cell killing or production of pro-inflammatory cytokines in response to foreign human leukocyte antigen (HLA, a cell surface antigen)-class 1 molecules. The trophoblast has protective mechanisms to avoid provoking a maternal alloimmune reaction, including complete suppression of all major histocompatibility complex (MHC) expression in the syncytiotrophoblast that is exposed to maternal blood, and expression of only some HLAs in extravillous cytotrophoblast exposed to the maternal uterine decidua. Some paternal HLA antigens (HLA-C) are expressed within this extravillous cytotrophoblast, and maternal NK cells occasionally recognise these antigens in a couple-specific interaction. Activation of maternal NK cells then leads to trophoblast cell death, inflammation, endothelial activation and inhibition of trophoblast invasion (Redman & Sargent, 2010; Sibai et al., 2005). This exaggerated maternal response requires a particular combination of maternal genetic factors and paternal antigens, demonstrating that unique couple-specific immune maladaptations may contribute to the development of pre-eclampsia (Duckitt & Harrington, 2005; Ness & Sibai, 2006; Sibai et al., 2005).

The maternal immune system is also involved with mediating the release of angiogenic growth factors. In normal pregnancy NK cells interact with the invading trophoblast resulting in substantial production of vascular endothelial growth factor (VEGF) and placental growth factor (PlGF). Pre-eclampsia (and FGR) pregnancies are associated with reductions in placental angiogenic factors, resulting in limited cytotrophoblast invasion (Bdolah, Sukhatme, & Karumanchi, 2004; Challis et al., 2009; Ness & Sibai, 2006). Alterations in levels of these angiogenic factors may also be mediated by transcription factors produced in response to reduced oxygen tension (e.g. hypoxia-inducible factor-1, HIF-1) that act to upregulate adaptive response genes. In the presence of these transcription factors, the cytotrophoblast responds to pro-inflammatory cytokines by increasing the production of soluble fms-like tyrosine kinase-1 (sFlt-1), a circulating receptor for the angiogenic growth factors VEGF and PlGF, Figure 3.11. This circulating receptor binds VEGF and PlGF making them unavailable for normal endothelial cell signalling (through cell-surface receptors FLT-1), resulting in vasoconstriction and endothelial dysfunction, Figure 3.11. In addition, sFlt-1 also has potent vascular endothelial actions which, in animal models, can independently produce both hypertension and proteinuria (Challis et al., 2009; Li et al., 2007). The magnitude of rise of sFlt-1 has been found to correlate well with disease severity, indicating the central role of angiogenic factors in the pathogenesis of pre-eclampsia (Sibai et al., 2005). Low levels of PlGF and high levels of sFlt-1 commonly precede the onset of pre-eclampsia (and FGR), and can sometimes be observed as early as the first trimester (Li et al., 2007; Ness & Sibai, 2006).

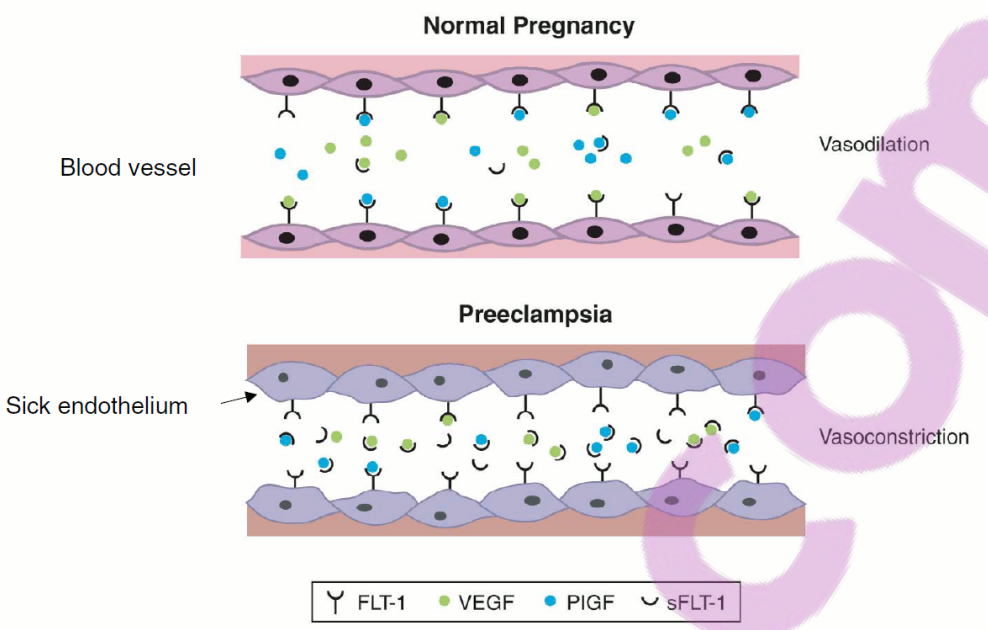


Figure 3.11 Mechanism of action of sFLT-1. During normal pregnancy, VEGF and PlGF signal through the VEGF receptors (FLT-1) and maintain endothelial health. In preeclampsia, excess sFLT-1 binds to circulating VEGF and PlGF, thus impairing normal signalling of both VEGF and PlGF through their cell-surface receptors. Thus, excess sFLT-1 leads to maternal endothelial dysfunction. Reprinted from Seminars in Nephrology, 24 (6), Bdolah et al., Angiogenic imbalance in the pathophysiology of preeclampsia: newer insights, 548-56, 2004, with permission from Elsevier.

Despite the central role of placental dysfunction in the pathogenesis of pre-eclampsia, it is also essential to note that the degree of severity between maternal, fetal and placental disease is not always concordant. Significant FGR can occur in the presence of mild pre-eclampsia (or without pre-eclampsia), while pre-eclampsia with severe maternal consequences can occur with a normally grown fetus. As a result, placental dysfunction can be considered only one of many interconnecting pathologies that include maternal factors and endothelial dysfunction, culminating in the phenotypic entity of pre-eclampsia (Callaway et al., 2009; Sibai et al., 2005).

Obesity, with pre-existing endothelial dysfunction as well as oxidative stress, inflammation, insulin resistance and immune maladaptation, shares many of the pathological features of the maternal response that results in pre-eclampsia. Additionally, the consequences of obesity (e.g. hypertension, diabetes/ insulin resistance) are themselves risk factors for pre-eclampsia and FGR indicating an overlap in pathophysiology between obesity and pre-eclampsia (Callaway et al., 2009; Ness & Sibai, 2006). The underlying reasons for increased rates of pre-eclampsia in obese women are likely multifactorial (not all obese women get pre-eclampsia, and pre-eclampsia also occurs in lean women) but probably relate to the level of pre-existing metabolic stress due to obesity, and the ability (or otherwise) to further compensate for the additional metabolic stressors of pregnancy.

Comparison of pre-eclampsia and FGR aetiologies

As previously mentioned FGR and pre-eclampsia share aetiological features however it is also clear that the maternal manifestations of these disorders are very different. Pre-eclampsia has an appreciable maternal component (which defines the syndrome) and may involve FGR, while FGR alone has no obvious immediate clinical impact on the mother. Although both diseases share poor placentation, pre-eclampsia is associated with a greater degree of endothelial dysfunction and inflammation than FGR, which suggests the possibility that pre-eclampsia may occur when there is an interaction between poor placental perfusion and maternal constitutional factors (Ness & Sibai, 2006).

It has been proposed that a common underlying disorder of both FGR and pre-eclampsia is a maternal predisposition to endothelial dysfunction (Ness & Sibai, 2006). This proposal is consistent with increased pre-eclampsia in women with pre-existing endothelial dysfunction e.g. hypertension, renal disease etc. as well as those with a family history of hypertension, coronary heart disease or cerebrovascular disease. It also helps to explain the association between FGR, pre-eclampsia and an increased risk of later cardiovascular morbidity and mortality (G. C. Smith et al., 2001; G. D. Smith et al., 2000). An underlying predisposition to endothelial dysfunction is also evident in obesity, insulin resistance and dyslipidaemic states, helping to explain the increased pre-eclampsia risk in obese women.

FGR and pre-eclampsia can be considered on the same spectrum of disease, where placental dysfunction progresses to maternal disease (manifesting as pre-eclampsia) when escalations in pregnancy-induced endothelial dysfunction crosses a clinical threshold. Pre-eclampsia in the absence of FGR may represent an exaggerated maternal response to pregnancy where placental features are less prominent. These processes could also be potentiated by a maternal alloimmune reaction as previously described.

Pre-eclampsia phenotypes

More recently it has been suggested that pre-eclampsia may consist of two separate phenotypes with aetiologies that differ; early- and late- onset pre-eclampsia (Huppertz, 2008; Vatten & Skjaerven, 2004; von Dadelszen, Magee, & Roberts, 2003). Early-onset pre-eclampsia, comprising 5-15% of all pre-eclampsia, is characterised by a preterm onset of disease with features suggestive of defective placentation. Significant placental dysfunction (evidenced by abnormal uterine artery Doppler studies) leads to secondary FGR and the severity of early-onset disease often results in preterm birth. In contrast late-onset pre-eclampsia, comprising >80% of all pre-eclampsia, occurs at term with normal or near-normal placental perfusion, commonly normal fetal growth, and is dominated by the maternal response to pregnancy (K. M. Groom, North, Poppe, Sadler, & McCowan, 2007; Huppertz, 2008; Vatten & Skjaerven, 2004; von Dadelszen et al., 2003; Xiong, Demianczuk, Saunders, Wang, & Fraser, 2002). This categorisation

also differentiates between different risk profiles for both the mother and fetus. For the mother, early-onset pre-eclampsia is associated with a considerable increase in risk of maternal morbidity and mortality, has a greater risk of recurrence in later pregnancies and a substantially increased risk of later cardiovascular disease and early death compared with late pre-eclampsia (Mongraw-Chaffin et al., 2010; von Dadelszen et al., 2003). For the fetus, early-onset pre-eclampsia is associated with an increased risk of FGR, preterm birth and associated perinatal morbidity and mortality (von Dadelszen et al., 2003). This classification is also supported by differences in maternal haemodynamics, cytokine production and insulin resistance in pregnancies affected by early- compared with late-onset pre-eclampsia (D'Anna et al., 2006; Valensise, Vasapollo, Gagliardi, & Novelli, 2008; von Dadelszen et al., 2003).

The phenotype of pre-eclampsia in obese women has been poorly characterised. As obesity has many features of the pre-eclampsia maternal response to pregnancy, there is a common perception that obesity predisposes to late-onset pre-eclampsia, however previous studies reporting rates of early- and late-onset pre-eclampsia among obese women are inconsistent (Mbah et al., 2010; Odegard, Vatten, Nilsen, Salvesen, & Austgulen, 2000; Rajasingam et al., 2009). One prospective study observed a greater increase in early- compared with late- onset pre-eclampsia in obese nulliparous women (25% of all pre-eclampsia was early-onset) (Rajasingam et al., 2009) while a Norwegian study showed a similar magnitude of increase in both early- and late-onset pre-eclampsia in women ≥70kg compared with <70kg (Odegard et al., 2000). Both of these studies involved small numbers of women. In contrast, a large retrospective study of >850,000 women showed a greater odds ratio association between obesity and late-onset pre-eclampsia (OR 2.97, 95%CI 2.90–3.04) compared to early-onset pre-eclampsia (OR 2.22, 95%CI 2.06–2.40) (Mbah et al., 2010). No studies have investigated other phenotypic aspects of early- and late-onset pre-eclampsia in obese women such as rates of SGA infants or abnormal uterine artery Doppler studies, and this is addressed in Chapter 8 of this thesis.

Consequences

The perinatal consequences of pre-eclampsia for both mother and infant have been mentioned previously and are substantial. As with FGR, there are long-term implications for the health of the mother of a pre-eclamptic pregnancy, but also for the infant. Infants of pre-eclamptic pregnancies have been exposed to the epigenetic programming associated with a combination of a hostile intrauterine environment that may have lead to FGR, as well as the effects of preterm birth. Females subsequently have an increased risk of pre-eclampsia themselves, while males have an increased risk of having a partner with a pre-eclamptic pregnancy, perpetuating another vicious cycle (Caughey et al., 2005; Dekker, 1999). Whether these associations are due to genetic heritable traits or epigenetic modulations is as yet unclear (Ness & Sibai, 2006; Sibai et al., 2005).

Management

As with FGR, the only management of pre-eclampsia occurs before pre-eclampsia is diagnosed. As previously discussed, prophylactic low-dose aspirin in early pregnancy likely results in improved trophoblast invasion and remodelling of the maternal spiral arteries, and early initiation of aspirin results in an overall risk reduction for pre-eclampsia of 17% (RR 0.83, 95% CI 0.77–0.89) (Duley et al., 2007) increasing to 53% (RR 0.47, 95% CI 0.34–0.65) in women at high risk of pre-eclampsia (e.g. pre-existing medical conditions and/or past history of severe pre-eclampsia) (Bujold et al., 2010). In addition calcium supplementation has been shown to reduce the risk of pre-eclampsia by approximately half, with the greatest risk reductions in women at high risk of pre-eclampsia (88% risk reduction RR 0.22, 95% CI 0.12–0.42) and women with low dietary calcium intake (64% risk reduction, RR 0.36, 95% CI 0.20–0.65) (Hofmeyr, Lawrie, Atallah, & Duley, 2010). Women with low calcium intake may have a higher blood pressure due to stimulation of parathyroid hormone or renin release and subsequent calcium uptake by smooth muscle leading to systemic vasoconstriction. Calcium supplementation therefore may reverse this sequence to reduce smooth muscle contractility. The use of calcium in pregnancy has been shown to impact directly on uteroplacental blood flow with reductions in Doppler resistive indices in both uterine and umbilical arteries (Carroli et al., 2010). Many other compounds have also been studied including magnesium supplements (Makrides & Crowther, 2001), dietary advice including protein supplementation (Kramer & Kakuma, 2003), fish oils (Makrides, Duley, & Olsen, 2006) and antioxidants (Rumbold, Duley, Crowther, & Haslam, 2008) although none have been found to have clinically useful reductions in risk.

Once pre-eclampsia has been diagnosed, there are no current therapies other than delivery that will reverse the progression of disease. Management involves close clinical observation enabling a balance between prolonging pregnancy to improve fetal outcomes (in the case of preterm gestations), while avoiding significant or severe maternal complications. Indications for delivery include a term gestation (≥37 weeks of gestation (Koopmans et al., 2009)), severe maternal complications (e.g. thrombocytopenia, deteriorating renal or hepatic impairment, pulmonary oedema, neurological dysfunction or placental abruption) or fetal concerns (e.g. severe fetal growth restriction with non-reassuring fetal monitoring) (S. A. Lowe et al., 2008; Solomon & Seely, 2006). Treatment with antihypertensives decreases the risk of severe hypertension and associated risk of intracerebral haemorrhage, but does not alter the course of the disease process (Duley, Henderson-Smart, & Meher, 2006).

Summary

Pre-eclampsia is an important cause of maternal morbidity and mortality worldwide, and obesity is associated with increased risk. The underlying causes of pre-eclampsia are still under

investigation however obesity, with pre-existing endothelial dysfunction and immune maladaptation, shares many of the pathological features of the maternal response seen in pre-eclampsia. Therefore it is possible that pre-eclampsia among obese women has a predominant late-onset pre-eclampsia phenotype, although this is not currently well characterised. Pre-eclampsia does not respond to therapy other than delivery of the placenta (and infant), however early recognition and timely delivery minimizes maternal morbidity. Understanding the risk factors for pre-eclampsia will aid clinicians to identify women who require increased pregnancy surveillance for pre-eclampsia.

3.4.3. Caesarean section and obesity

Maternal obesity has been associated with higher rates of labour dysfunction and an increasing risk of CS delivery with increasing BMI (Barau et al., 2006; Nuthalapaty, Rouse, & Owen, 2004; Vahratian, Zhang, Troendle, Savitz, & Siega-Riz, 2004). Importantly, this association is independent of important confounding factors such as infant birthweight and induction of labour. As obesity is also a risk factor for serious perioperative complications such as infection, deep vein thrombosis, wound dehiscence and postpartum haemorrhage (Fyfe, Thompson, Anderson, Groom, & McCowan, 2012; Liston & Davies, 2011; Modder J, Fitzsimons KJ, & on behalf of the Centre for Maternal and Child Enquiries and the Royal College of Obstetricians and Gynaecologists, 2010; Myles, Gooch, & Santolaya, 2002), it is important to understand why obese women have increased CS risk.

Rising Caesarean section rates

Labour is a complex process that ends with the birth of the infant and placenta. For labour to be successful (the vaginal birth of a healthy infant without harm to the mother) the fetus must navigate through the small dimensions of the maternal pelvis by means of efficient coordination of uterine contractions and associated cervical dilation. Increasingly however infants are not born vaginally but by CS, with rates reaching up to 50% in some private obstetric populations (J. Villar et al., 2006). CS is now the most prevalent obstetric intervention and can be associated with serious maternal morbidity and even mortality, especially in women with co-morbidities such as obesity.

Historically CS was performed in labour to save mother's lives, however was associated with severe maternal morbidity and occasionally death (Ecker & Frigoletto, 2007). Improved operative safety over time means CS is now less hazardous for the mother, and therefore CS is increasingly performed for fetal reasons resulting in improved perinatal outcomes (Althabe et al., 2006; Betran et al., 2007). More recently, escalating CS rates in developed countries have been a cause for concern due to an increase in associated maternal morbidity compared with a vaginal birth, without a corresponding decrease in perinatal mortality or morbidity (Betran et al., 2009; Lumbiganon et al., 2010). High CS rates are not only associated with increased

maternal morbidity, but lately have also been shown to be associated with increased neonatal morbidity and mortality (Jose Villar et al., 2007). An optimum CS rate for a population would balance the risks of maternal and neonatal morbidity and mortality, however it remains unclear what this optimum CS rate should be.

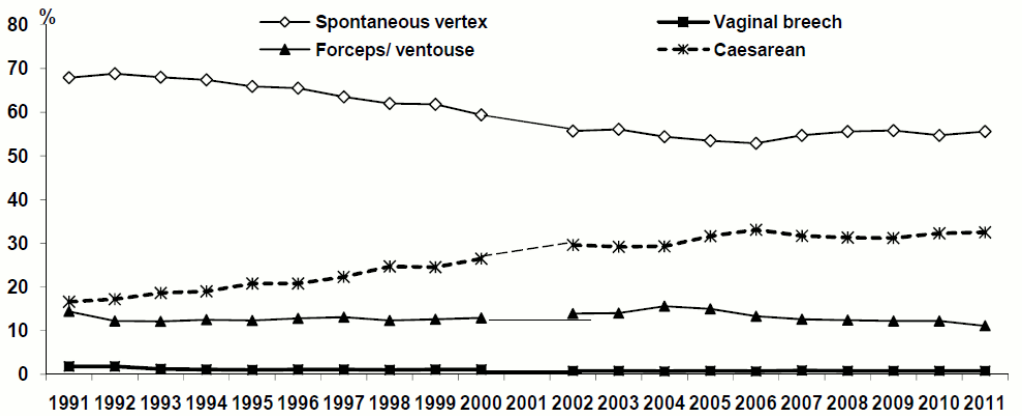


Figure 3.12 Mode of birth at National Women's Health 1991-2011. Reproduced with permission National Women's Health, 2012.

Rising CS rates have also been observed locally; at NWH in 2011 33% of all births were via CS compared to 17% in 1991, Figure 3.12 (National Women's Health, 2012). Reasons for these rising CS rates are multi-factorial, including changing indications for CS (e.g. breech presentation), increased procedural safety, greater numbers of high risk pregnancies as well as patient and caregiver preference (Hannah et al., 2000; Stjernholm, Petersson, & Eneroth, 2010; Thomas et al., 2001). The greatest overall contributor to CS rates are women with a previous CS delivery (Betran et al., 2009; National Women's Health, 2012), corresponding with declining rates of vaginal birth after caesarean (VBAC), Figure 3.13 (Ecker & Frigoletto, 2007; MacDorman, Menacker, & Declercq, 2008; National Women's Health, 2012). A major contributor to repeat CS rates however is a substantial rise in primary CS rates, particularly among primiparous women, Figure 3.13 (MacDorman et al., 2008; Minkoff & Chervenak, 2003; Stavrou, Ford, Shand, Morris, & Roberts, 2011).

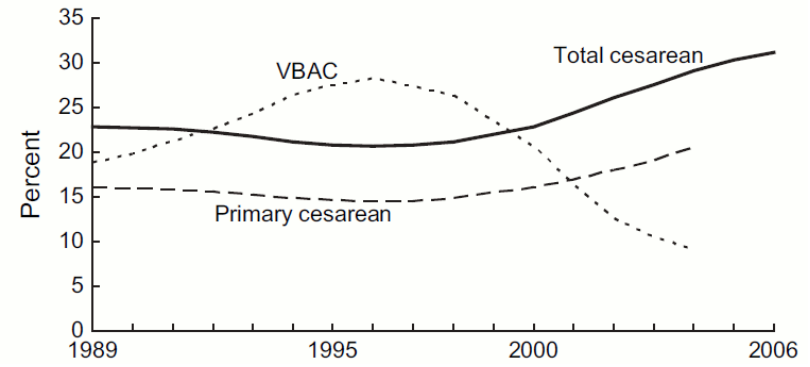


Figure 3.13 Primary and total Caesarean section rates and rate of vaginal birth after previous Caesarean section (VBAC) in the United States. Reprinted from Clinics in Perinatology, 35, MacDorman et al., Cesarean Birth in the United States: Epidemiology, Trends, and Outcomes, 293-307, 2008, with permission from Elsevier.

These trends are also illustrated in data from New South Wales, Australia where significant trends of increasing CS rates have been observed among women with a previous CS, and elective CS at term among nulliparous women, Figure 3.14. Contemporaneously, there appears to be an increase in CS performed at patient request (Minkoff & Chervenak, 2003; Robson, Tan, Adeyemi, & Dear, 2009; Wagner, 2000), where 'maternal request' was the fifth most common indication for elective CS in the UK in 2001 (Thomas et al., 2001). Conversely, women who have a successful vaginal birth in their first pregnancy are much less likely to have a CS in future pregnancies (illustrated by the low CS rate among 'All multiples' in Figure 3.14), and therefore research that focuses on preventing primary CS is likely to have a substantial impact on overall CS rates.

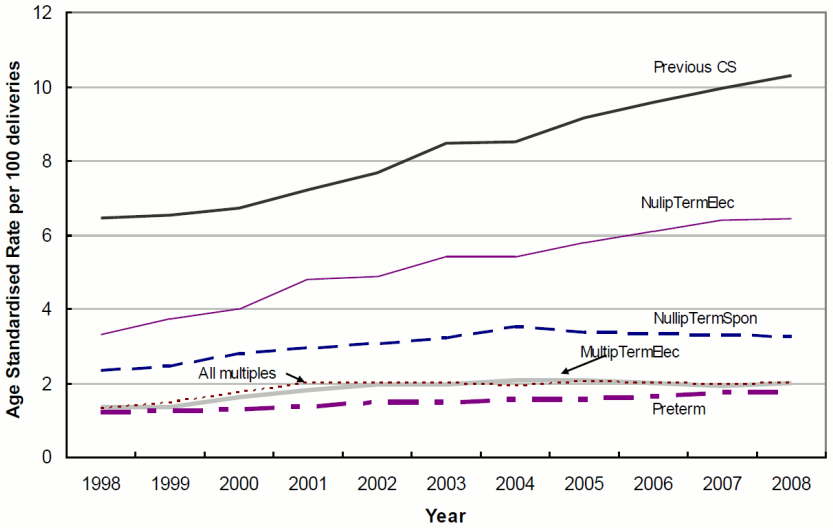


Figure 3.14 Age-standardised rate of CS delivery per year, 10-group classification, NSW, 1998-2008. Reprinted from BMC Pregnancy and Childbirth, 11 (8), Stavrou et al. Epidemiology and trends for Caesarean section births in New South Wales, Australia: A population-based study, 2011, under the terms of the Creative Commons Attribution License. http://www.biomedcentral.com/1471-2393/11/8.

Increases in CS rates have also coincided with increasing obesity rates in obstetric populations. As previously mentioned there is a well-established linear association between CS rate and pre-pregnancy BMI. This increased risk of CS has been associated with ineffective uterine activity (Cedergren, 2009; J. Zhang, Bricker, Wray, & Quenby, 2007) and labour dysfunction, particularly poor labour progression or arrest of cervical dilatation (Verdiales, Pacheco, & Cohen, 2009). Poor *in vitro* uterine contractility has been demonstrated in myometrial samples from obese women taken at elective CS (J. Zhang, L. Bricker, et al., 2007), and it has been hypothesised that metabolic factors such as abnormal maternal lipids (J. Zhang, Kendrick, Quenby, & Wray, 2007), and/ or leptin (Moynihan, Hehir, Glavey, Smith, & Morrison, 2006) may inhibit myometrial contractility. Recent studies investigating the timing of CS in labour, have observed that CS in obese women are predominantly performed in the first stage of labour, and those women that reach the second stage of labour are just as likely to have a vaginal birth as normal weight women (Buhimschi, Buhimschi, Malinow, & Weiner, 2004; Fyfe et al., 2011). These findings suggest that obese women with impaired myometrial contractility are identified in first stage by poor progress/ obstructed labour and therefore do not reach the second stage of labour. However a further study of the first stage of labour has shown that although obese women had longer labours and were more likely to have CS, they also achieved equivalent intrauterine pressures (a measure of the force of contractions) as normal weight women (Chin, Henry, Holmgren, Varner, & Branch, 2012). The reasons for greater CS in obese women remain uncertain.

Confounders of obesity and Caesarean section

Pregnancies to obese women have features that potentially confound the risk of CS. As such it is important to allow for these factors when investigating CS rates among obese women. Both increased infant birthweight and increased rates of SGA in obese women have been discussed previously, and birthweight has a U-shaped association with increased risk of CS; i.e. a higher risk of CS with small and large infants (G. C. Smith, 2000). In addition, obese women may also be at increased risk of prolonged (>41 weeks gestation) and post-term (>42 weeks gestation) pregnancy (Caughey, Stotland, Washington, & Escobar, 2009; Denison, Price, Graham, Wild, & Liston, 2008), where post-term pregnancy is independently associated with an increased risk of fetal macrosomia, induction of labour and CS (J. M. Alexander, McIntire, & Leveno, 2001). Pregnancy complications such as diabetes or hypertensive disease are more common in obese mothers as previously discussed, and women with these complications are more likely to require induction of labour. Labour induction may be an independent risk factor for CS, particularly among obese and/ or nulliparous women (Ehrenthal, Jiang, & Strobino, 2010; Gulmezoglu, Crowther, & Middleton, 2006; Heffner, Elkin, & Fretts, 2003; Wolfe, Rossi, & Warshak, 2011).

Obesity is currently associated with increasing age, and a maternal age >35y has been associated with elevated rates of both elective and emergency CS (Lin, Sheen, Tang, & Kao, 2004; G. C. Smith et al., 2008). Advanced maternal age is in turn confounded by socio-economic status as affluent women (who are less likely to be obese) are increasingly likely to delay childbearing, and high rates of both elective and emergency CS occur among wealthy women who have private obstetric care (Alves & Sheikh, 2005; Barley, Aylin, Bottle, & Jarman, 2004; Thomas et al., 2001). However the association between obesity and increasing maternal age may change in the near future as younger women gradually become more overweight (Swinburn et al., 2011; World Health Organization, 2000). Maternal height is also a predictor of CS risk, with short stature associated with increased risk, and tall stature associated with decreased risk (Jensen, Agger, & Rasmussen, 2000; McGuinness & Trivedi, 1999). Although maternal height by definition is closely correlated with BMI, it remains an independent risk factor for CS (Barau et al., 2006). Few studies include both BMI and maternal height in analyses of CS risk factors.

Consequences of CS

CS is an intervention intended to improve outcomes for mothers and babies, however increasingly CS has been associated with harm to both. Birth is a time of transition for the fetus, and the physiological stressors of labour assist in this transition. Elective CS therefore is associated with an increased chance of the infant failing to adapt to the external environment by way of increased respiratory complications, particularly respiratory distress syndrome (RDS) and transient tachypnoea of the newborn (Hansen, Wisborg, Uldbjerg, & Henriksen, 2008; J. J. Morrison, Rennie, & Milton, 1995). Labour and vaginal birth however can cause hypoxic or physical injury to the infant, particularly in the case of breech vaginal birth (Hannah et al., 2000) or macrosomia (Vidarsdottir, Geirsson, Hardardottir, Valdimarsdottir, & Dagbjartsson, 2011), and current methods of intrauterine fetal wellbeing monitoring have poor sensitivity for detecting fetal hypoxaemia (Alfirevic, Devane, & Gyte, 2006). CS also has well-established immediate and long-term negative consequences for the mother. Risks include increased peripartum blood loss and risk of post-partum haemorrhage, damage to pelvic organs, wound infection, respiratory and urinary infection, venous thromboembolism, increased pain, delayed onset of lactation and decreased breastfeeding rates as well as longer hospitalisation (Belizan, Althabe, & Cafferata, 2007; Ecker & Frigoletto, 2007). Of concern, obese women are at substantially increased risk of all of these CS complications compared with women of normal weight (Centre for Maternal and Child Enquiries (CMACE), 2010; Modder J et al., 2010). In pregnancies that follow a CS delivery there are small increases in the risk of miscarriage, ectopic pregnancy, placenta previa, placenta accreta and stillbirth (Ecker & Frigoletto, 2007; Gilliam, 2006). Elective CS potentially has benefits for the mother in that it has been shown to be protective of postpartum urinary incontinence and genital organ prolapse (Sze, Sherard, &

Dolezal, 2002), however the greatest predictor of these conditions is age, and as such this protective association gets smaller or disappears with increasing age (Minkoff & Chervenak, 2003). In the same way there are no good quality data that CS is protective of anal incontinence (Nelson, Furner, Westercamp, & Farquhar, 2010). Overall, for the majority of women CS is associated with more maternal and neonatal harm than benefit, however the decision for CS is complex and includes assessment of maternal and fetal wellbeing as well as maternal and caregiver preference.

Summary

CS rates are increasing in developed countries without further improvements in perinatal mortality or neonatal morbidity, and high CS rates are likely to be harmful to both mother and infant. This rise in CS prevalence is occurring at a time when obesity prevalence is also increasing among maternity populations, where obesity has a strong independent association with risk of CS. The consequences of CS include both immediate and long-term complications for the mother and future pregnancies, and the risk of complications can be substantially increased among obese mothers.

3.4.4. Minimising obesity-related adverse pregnancy outcomes

Obese mothers, with an increased risk of multiple complications of pregnancy, should be managed as high-risk pregnancies. The improvement of pregnancy outcomes for these women has previously focussed on pre-pregnancy weight loss however this does not help women who are already pregnant. Guidelines on GWG in pregnancy have suggested pregnancy outcomes are improved for those obese women who achieve limited GWG in pregnancy (Nohr et al., 2009; Rasmussen & Yaktine, 2009).

Pre-pregnancy weight loss/ bariatric surgery

Studies investigating adverse pregnancy outcomes in obese mothers have commonly concluded that obese women should be counselled about obesity-related pregnancy risk and advised to lose weight prior to conception (Centre for Maternal and Child Enquiries (CMACE), 2010; Dixit & Girling, 2008; Gunatilake & Perlow, 2011). Chapter 2 of this thesis has outlined the biological and behavioural difficulties associated with weight loss, and unsurprisingly weight loss programmes are typically unsuccessful in the long term, with only 2-5% of adults maintaining substantial weight loss at two years (Catalano & Ehrenberg, 2006; Simpson, Shaw, & McNamara, 2011). Additionally, as up to half of all pregnancies are unplanned, pre-pregnancy counselling is not possible for many women (Stotland, 2008).

A growing body of evidence suggests that the most effective and enduring mechanism of weight loss in morbidly obese adults is bariatric surgery (Elder & Wolfe, 2007; Simpson et al., 2011). Differing bariatric procedures have differing long-tem weight loss results, with less complex procedures having lower success rates but also lower complication rates. A meta-analysis of

bariatric surgical procedures estimated that the mean percentage loss of excess weight at two years following surgery for all bariatric surgery procedures was 61.2% (95% CI 58.1%– 64.4%), ranging from 47.5% for gastric banding to 70.1% for more complex procedures such as biliopancreatic diversion or duodenal switch (Buchwald et al., 2004). Women who become pregnant after bariatric surgery require surveillance for nutritional deficiencies associated with the increased demands of pregnancy, but have a reduced risk of adverse pregnancy outcomes compared to obese mothers, with overall rates of adverse pregnancy outcomes approximating those of the general population (J. B. Dixon, Dixon, & O'Brien, 2005; Sheiner et al., 2004).

Weight loss associated with bariatric surgery also improves the intrauterine environment for the fetus. Studies in women with pregnancies before and after bariatric surgery have shown dramatic differences in offspring outcomes. Infants of obese women born after bariatric surgery had lower birthweights, less childhood and adult obesity and significant improvements in cardio-metabolic markers compared with their siblings born prior to bariatric surgery (Kral et al., 2006; J. Smith et al., 2009). Importantly there were also no recognised adverse outcomes for the offspring associated with maternal bariatric surgery. Bariatric surgery can therefore be safely recommended for morbidly obese women prior to pregnancy to improve pregnancy outcomes.

Gestational weight gain

The components of normal GWG include the fetus, placenta and amniotic fluid as well as maternal increases in blood volume, interstitial fluid, uterine and breast tissue along with increased fat mass (Rasmussen & Yaktine, 2009). Serial assessments of weight throughout pregnancy have traditionally been performed to ensure women gain sufficient weight, where low GWG is associated with adverse pregnancy outcomes such as preterm birth and SGA infants (Committee on Nutritional Status During Pregnancy and Lactation & Institute of Medicine, 1990; Viswanathan et al., 2008). Increasingly however, women are gaining excess weight in pregnancy with >20% of American women gaining >18kg (more than the recommended weight gain for underweight women, Table 3.1)(Rasmussen & Yaktine, 2009). Excess GWG has an adverse impact on pregnancy outcomes, particularly among obese women (Cedergren, 2007; Nohr et al., 2008; Rasmussen & Yaktine, 2009).

Regardless of initial BMI, excess GWG is associated with an increased risk of excess fetal growth and macrosomia, CS and postpartum weight retention, and may also be associated with gestational diabetes and hypertensive diseases of pregnancy (Carreno et al., 2012; Cedergren, 2006; Nohr et al., 2009; Rasmussen & Yaktine, 2009; Viswanathan et al., 2008). Post partum weight retention has been shown to be a significant driver of obesity in women because of a progressive spiral of subsequent pregnancies with increasingly high BMIs; i.e. increasing BMI between pregnancies leading to obesity-related complications in subsequent pregnancies,

including further excess GWG and postpartum weight retention (Getahun, Ananth, et al., 2007; Getahun, Kaminsky, et al., 2007). The increased risk associated with high GWG are exacerbated by pre-pregnancy obesity, but importantly they can also be ameliorated by limited GWG (Nohr et al., 2009; Rasmussen & Yaktine, 2009). Obese women with limited weight gain be at lower risk for some complications (e.g. macrosomia) than a normal weight woman with excess GWG (Nohr et al., 2009; Rasmussen & Yaktine, 2009). However, very limited GWG (<5kg) has been associated with higher rates of SGA (defined by both population and customised birthweight standard) in all BMI groups (Dietz, Callaghan, Smith, & Sharma, 2009; Rasmussen & Yaktine, 2009). Gestational weight loss in one retrospective observational study was associated with increased SGA and preterm birth in all but obese class III (BMI ≥40kg/m^2) mothers (Beyerlein, Schiessl, Lack, & Von Kries, 2011). As very limited GWG or gestational weight loss in pregnancy can be associated with metabolic abnormalities such as ketonaemia, and studies in women with diabetes have shown elevated ketones are inversely associated with intellectual development of children at 3-5 years of age, very low GWG or gestational weight loss in pregnancy cannot currently be recommended (Rasmussen & Yaktine, 2009).

After a thorough review of literature, in 2009 the Institute of Medicine in the USA updated recommendations for total GWG by maternal BMI, Table 3.1. It is important to note that these recommendations are for total weight gain based on a BMI calculated from pre-pregnancy weight. Studies of GWG and maternal weight/ BMI in pregnancy commonly use self-reported pre-pregnancy weight to calculate BMI due to the inherent difficulties of measuring weight in women who are not yet pregnant. Pregnant women have been shown to underestimate their height and weight on self-report, which can lead to systematic bias in assessing obesity-related effects (Bodnar, Siega-Riz, Simhan, Diesel, & Abrams, 2010; B. M. Craig & Adams, 2009; Gaudet, Gruslin, & Magee, 2011). Those studies that used measured weight in early pregnancy were adjusted for an average of 0.5–2 kg (1.1–4.4 lbs) weight gain in the first trimester, based on observational studies in normal pregnancy (Abrams, Carmichael, & Selvin, 1995; Carmichael, Abrams, & Selvin, 1997; Siega-Riz, Adair, & Hobel, 1994). Notably most research on GWG has been retrospective observational studies and therefore causality cannot be attributed. Weight is a coarse measurement tool and is influenced by all of the components of GWG as previously mentioned. Increased weight may be due to increased maternal adiposity leading to increased fetal growth, or increased fetal growth may result in increased GWG. Conversely low GWG may not cause FGR, but result from poor fetal growth. Women with low GWG may also have other reasons for limited weight gain e.g. illness, stress etc. It is also unclear how other pathological components contribute to maternal weight e.g. excess interstitial fluid in pre-eclampsia. Despite these limitations the Institute of Medicine recommendations are based on a comprehensive review and synthesis of the literature in this area.

Table 3.1. Recommendations for total weight gain during pregnancy, by prepregnancy body mass index (BMI). (Rasmussen & Yaktine, 2009)

Prepregnancy BMI	Total weight gain range (kg)
Underweight (<18.5 kg/m^2)	12.5-18
Normal weight (18.5-24.9 kg/m^2)	11.5-16
Overweight (25.0-29.9 kg/m^2)	7.0-11.5
Obese (≥ 30.0 kg/m^2)	5.0-9.0

In contrast to the above recommendations, the UK National Institute for Health and Clinical Excellence (NICE) guidelines for weight management in pregnancy (National Institute for Health and Clinical Excellence, 2010) have not advised regular weighing of pregnant women as there currently is no evidence for an effective intervention to improve clinical outcomes (Poston & Chappell, 2012). Prospective research on limiting GWG in obese mothers has had mixed success; a recent meta-analysis was limited by heterogenous data reporting and quality of data issues, however interventions (particularly dietary and to a lesser extent exercise interventions) seem to be somewhat successful in limiting GWG in obese women and are not unsafe (Tanentsapf, Heitmann, & Adegboye, 2011; Thangaratinam et al., 2012). What remains unclear is whether this limited GWG translates into clinically important outcomes. In these prospective trials. lower GWG in obese women has not been found to impact on fetal weight or CS rates, and although lower rates of gestational hypertension, pre-eclampsia and gestational diabetes have been observed, the quality of evidence for these outcomes is low (Thangaratinam et al., 2012). Long term post-partum weight retention may be lower in women who received dietary advice in pregnancy (Tanentsapf et al., 2011), and this may help to interrupt the vicious cycle of subsequent pregnancies with increasingly high BMIs.

Summary

The risk of obesity-related adverse outcomes can be reduced by pre-pregnancy weight loss, however spontaneous weight loss in obese adults has poor long-term success. Pre-pregnancy bariatric surgery improves pregnancy outcomes for morbidly obese women, and has better long-term success for permanent weight loss. Pregnant obese women may be able to reduce their risk of adverse pregnancy outcomes by limiting GWG, while excess GWG is associated with adverse pregnancy outcomes regardless of pre-pregnancy BMI. Excess GWG is also associated with an increased chance of post-partum weight retention, which may lead to a cycle of increasing BMI in subsequent pregnancies; a potent driver of adult obesity in women.

3.5. Financial and resource implications of obesity in pregnancy

With excess maternal adiposity now common in obstetric populations and associated with an increased risk of pregnancy complications and interventions, maternal obesity has major resource and financial implications for health services. There are also particular technical

challenges associated with monitoring for complications among obese women, such as difficult fetal assessment (both clinically and through ultrasound), difficulties with venesection and accurate blood pressure assessment etc. (Rowlands, Graves, de Jersey, McIntyre, & Callaway, 2010). Obese women have more ultrasound examinations, are more likely to need obstetric as well as anaesthetic specialist review and have higher chance of antenatal and postnatal hospital admission with longer durations of stay than women of normal weight (Chu et al., 2008; Heslehurst, Lang, et al., 2007; Heslehurst et al., 2008). A prospective French study estimated that the cost of hospitalisation for women with a BMI >26kg/m^2 was approximately five times greater than for women of normal weight (Galtier-Dereure, Boegner, & Bringer, 2000). However hospitalisation is only part of the cost of obesity in pregnancy. Morbidly obese women may also require specialist equipment e.g. bariatric beds and wheelchairs, specialist lifting or operating theatre equipment etc. (Catalano & Ehrenberg, 2006; Rowlands et al., 2010).

Maternal overweight and obesity affects approximately 35% of the NWH obstetric population and approximately 7.5% of women have a BMI >35kg/m^2 (National Women's Health, 2012). Although comprehensive BMI data are not currently part of national NZ maternity reporting, extrapolating NWH data to all NZ births per annum (approximately 65 000 births per year, (Ministry of Health, 2011)) 22 750 births would occur every year to overweight or obese mothers, with 4875 births per year to morbidly obese mothers. With this prevalence, even a small increase in healthcare cost associated with maternal obesity has substantial economic implications to the NZ healthcare system, and the costs associated with the above complications of pregnancy are not insignificant. The prevention of obesity or intervention among women of childbearing age through public health initiatives (including possibly the provision of bariatric surgery) will not only improve the health of the targeted women, but also prevent epigenetic transmission of metabolic consequences to the next generation (Atkinson, Pietrobelli, Uauy, & Macdonald, 2012).

Chapter 4. | Ethnicity and pregnancy

4.1. Introduction

Ethnicity can be considered a social construct whereby an individual associates themselves with others that have similar cultural or ideological characteristics based on a sense of common origins (Ministry of Health, 2004a). The concept of ethnicity is complex, multi-factorial and fluid; self-reported ethnicity may change for an individual over time. Categorizing people into ethnicities is a coarse but useful way of attempting to identify differences between groups that are likely to have similar characteristics at a population level. The importance of this in NZ is evidenced by continuing reports of ethnic inequalities, including in healthcare, with Māori and Pacific peoples particularly disadvantaged (Human Rights Commission, 2012).

Maternal ethnicity may modify the risk of adverse pregnancy outcomes however in contrast to obesity, there are relatively few studies investigating ethnicity in pregnancy. International studies that address ethnicity in pregnancy generally report increased rates of complications in non-European ethnicities, particularly in Western countries (Gregory & Korst, 2003; Hessol & Fuentes-Afflick, 2005; Ramos & Caughey, 2005; Thomas et al., 2001). In NZ there are limited data on ethnicity and obstetric outcomes, however NZ maternity reports and the small number of NZ studies available consistently show a discrepancy between higher rates of adverse pregnancy outcomes in Māori and Pacific women (such as rates of SGA infants and stillbirth) but decreased rates of obstetric interventions (E. D. Craig, Mantell, Ekeroma, Stewart, & Mitchell, 2004; Harris et al., 2007; Sadler, McCowan, & Stone, 2002). Data limitations raise uncertainties about the validity of ethnic differences in obstetric outcomes, with most studies not able to adjust for important confounding factors such as BMI. As the prevalence of obesity varies greatly between ethnic groups, this important confounder may account for a substantial proportion of the differences seen between ethnicities. Other clinical confounders such as parity, age, socioeconomic factors, smoking or maternity caregiver may explain observed discrepancies in obstetric outcome between ethnicities, however it remains possible true ethnic differences exist.

4.2. Definition of ethnicity

As mentioned, ethnicity is a complex concept of self-perceived cultural affiliation. In NZ, the definition of ethnicity adopted by Statistics New Zealand follows:

An ethnic group is made up of people who have some or all of the following characteristics:

- *a common proper name*
- *one or more elements of common culture which need not be specified, but may include religion, customs, or language*
- *unique community of interests, feelings and actions*
- *a shared sense of common origins or ancestry, and*
- *a common geographic origin.*

(Statistics New Zealand, 2005)

An individual may identify with some or all of these characteristics at different times which can result in changing ethnic affiliations. People can also belong to more than one ethnic group at a time. As a consequence it is unlikely others would be able to accurately choose an individual's ethnic group meaning self-reported ethnic affiliation is vital for accurate data collection (Statistics New Zealand, 2004).

Contributors to an individual's concept of ethnicity may include considerations such as ancestory, race, culture, and nationality (Callister, Didham, & Kivi, 2009; Ministry of Health, 2004a). Ancestry can be considered the people from whom the individual is descended, and is interrelated with the concept of race. Race has been defined as 'the descendants of a common ancestor especially those who inherit a common set of characteristics; such a set of descendants, narrower than a species; a breed; ancestry; lineage, stock; a class or group, defined otherwise than by descent' (Ministry of Health, 2004a). Social perceptions of race commonly involve physical characteristics such as skin colour, however there are no biological characteristics by which humans can reliably be grouped according to race (R. S. Schwartz, 2001). A person's culture can be defined as the manner in which they live day-to-day, consisting of language, religion, values and beliefs, family life, cuisine, music etc (Callister et al., 2009), while a person's nationality is the sense of belonging to a particular nation, whether that results from being born in that nation or through immigration and citizenship etc. While these factors contribute to a person's determination of ethnic affiliation, they do not necessarily define ethnicity for that individual (Ministry of Health, 2004a).

In NZ, the rationale behind official ethnicity statistics is the recognition that social and economic inequality exists between ethnic groups. The collection of ethnicity data therefore allows for quantification of inequalities which then allows for targeting of intervention, funding, public initiatives etc. This rationale aligns with many other Western countries e.g. the USA, UK, Canada and Australia (Morning, 2008). Ethnicity data used in NZ healthcare reports and analyses undergoes a prioritisation procedure, whereby if an individual reports more than one ethnicity they are allocated to a single prioritised ethnic group based on a predefined system. This

procedure prioritises ethnicities in the order of Māori, Pacific peoples, Asian, other ethnic groups and NZ European (Ministry of Health, 2004a). The choice of prioritised ethnicity simplifies ethnicity reporting to provide an overall national standard that allows for robust comparisons to be made between reports or studies (Ministry of Health, 2004a). Philosophically, prioritisation aims to ensure that ethnic groups that are of particular importance or of small size are not overwhelmed by the NZ European ethnic group. In the case of Māori and Pacific peoples prioritisation recognises Māori as having a unique place in NZ society as the *tangata whenua* (indigenous population) and that government has an important role in working to ensure Māori have the same health status as non-Māori, along with protecting Māori cultural values and practices. With regards to Pacific peoples, prioritisation recognises the contributions Pacific peoples have had to NZ society, the predicted increases in the proportion of individuals of Pacific descent, as well as identifying them as having poorer on average health status (Ministry of Health, 2004a). This prioritisation procedure is acknowledged to have limitations particularly that it biases statistics by over-representing Māori and Pacific peoples at the expense of other ethnic groups and goes against the principle of self-determination. Ethnicity codes and prioritisation details can be found in Appendix 1.

4.3. Health and ethnicity

Disparities in health outcomes between ethnic groups have long been observed (Kenealy et al., 2008; Knight, Kurinczuk, Spark, Brocklehurst, & Ukoss, 2009; R. S. Schwartz, 2001). In NZ, ethnic inequalities are particularly evident among Māori and Pacific peoples, whose health status is on average lower than that of other New Zealanders (Human Rights Commission, 2012; Ministry of Health, 2004a; Statistics New Zealand, 2004). Metabolic complications associated with adiposity have been noted to have substantial ethnic disparities, i.e. disorders such as dyslipidaemia, hypertension, insulin resistance and associated coronary heart disease, cerebrovascular disease and diabetes (Bhopal, Rahemtulla, & Sheikh, 2005; Hodge et al., 2010; McKeigue, Miller, & Marmot, 1989; McKeigue et al., 1991; Winkleby, Kraemer, Ahn, & Varady, 1998). One explanation of these associations is that people with the same ethnic affiliation have similar lifestyle and behavioural characteristics, and as a result often have similar healthcare-related issues or concerns. For example, smoking rates among NZ Māori are substantially higher than in other NZ ethnic groups (Ministry of Health, 2009b; The Quit Group and the Ministry of Health, 2009). Other demographic ethnic associations that impact on health outcomes include increased poverty, lower education status (Ministry of Health, 2010; White, Gunston, Salmond, Atkinson, & Crampton, 2008; Winkleby et al., 1998), cultural factors (e.g. differences in attitude to food) (Bruss et al., 2005; University of Otago and Ministry of Health, 2011) and cultural and language

barriers to accessing healthcare (particularly among new immigrant populations) (Alderliesten, Vrijkotte, Van Der Wal, & Bonsel, 2007; Human Rights Commission, 2012; R. S. Schwartz, 2001).

However, as already mentioned there are also measurable ethnic differences in body composition, including lean body mass to adipose ratios as well as differing distributions of body fat for the same BMI (Rush et al., 2004; Swinburn et al., 1999; J. C. Wells, 2012; World Health Organization expert consultation, 2004). Body fat distribution is particularly important as visceral adipose tissue is more 'metabolically active' than subcutaneous adipose tissue (Despres & Lemieux, 2006; Eckel, Alberti, Grundy, & Zimmet, 2010; Müller et al., 2012) (see also sections 2.2, 2.5.6 and Figure 2.5 above). Ethnic groups with a predisposition for accumulation of adiposity in a visceral distribution are at increased risk of obesity-related health conditions. Indian and Asian populations have been observed to have high rates of visceral adiposity (even though they may not be obese by WHO BMI criteria), while Pacific populations may have more subcutaneous adiposity compared with European (McKeigue et al., 1991; Wang et al., 1994; WHO/IASO/IOTF, 2000). These ethnic differences may help to explain the varying associations between BMI and metabolic risk factors by ethnicity. For example, Chinese adults have a high prevalence of hypertension, diabetes and dyslipidaemia at BMI indices below the WHO cut-off point for overweight (BMI 25kg/m^2) (Chiu, Austin, Manuel, Shah, & Tu, 2011; Cockram et al., 1993; Deurenberg-Yap & Deurenberg, 2003; Ko et al., 1999). Similar observations have been made in other populations, for example increased rates of hypertensive disease, metabolic syndrome, cardiovascular disease and diabetes among Asian, Indian, African and Hispanic populations at lower BMIs when compared with European populations (Colin Bell et al., 2002; Davis, 2008; Palaniappan, Wong, Shin, Fortmann, & Lauderdale, 2011). As the WHO BMI classifications were created using European populations, these observations suggest that standard WHO criteria may not be appropriate to define adiposity-related risk for all ethnicities (see section 2.2 above) (WHO/IASO/IOTF, 2000).

Ethnic-specific BMI categories have been proposed (Table 2.2) that account for both differing levels of adiposity, and adiposity-related risk between ethnicities. The recommendations for Asian and Indian BMI categories are based on multiple international reports that have investigated the risk of adiposity-related disease. BMI category recommendations for Māori and Pacific populations are based solely on comparisons of adiposity between Māori, Pacific and European adults, with no further studies relating the degree of adiposity to risk of adverse health outcomes in either of these ethnic groups (Swinburn et al., 1999; WHO/IASO/IOTF, 2000; World Health Organization expert consultation, 2004).

Strong associations between ethnicity and adverse health outcomes have been observed in NZ for some time, (Human Rights Commission, 2012; Ministry of Health, 2008) however few NZ multivariable studies accounting for health-related confounders of ethnicity have been

performed. In particular, few studies have been able to account for BMI despite national health reports consistently showing high rates of overweight and obesity among Māori and Pacific peoples, and lower rates among Asian/ Indian ethnicities compared with European (WHO criteria, Table 2.1)(Ministry of Health, 2004b, 2008). Pacific peoples in NZ have been observed to have significantly higher rates of cardiovascular disease risk factors including hypertension and diabetes (Grey et al., 2010) and Māori and Pacific peoples both have increased coronary heart disease morbidity and mortality compared with NZ European (Bell et al., 1996), however these data are not adjusted for BMI. A single study of cardiovascular risk factors among NZ ethnicities found that differences in rates of hypertensive disease between ethnic groups were almost eliminated after adjusting for BMI (Bullen et al., 1996), highlighting the importance of including BMI in analyses.

The complex relationship between ethnicity and health outcomes is not easily addressed. However to improve health outcomes for all ethnic groups, it is vital to ensure that research into ethnic disparities includes adequate assessment of ethnicity-related confounders. In NZ, this particularly applies to the use of BMI data.

4.4. Ethnicity and pregnancy outcomes

Along with increased rates of poor health outcomes, ethnicity has associations with adverse pregnancy outcomes, with minority ethnic groups usually at increased risk (Caughey et al., 2005; Leung et al., 2008; Ramos & Caughey, 2005; Rao, Daniels, El-Sayed, Moshesh, & Caughey, 2006; Thomas et al., 2001). Again, most studies investigating ethnicity and pregnancy outcomes use national or regional databases that do not include BMI data, and also rarely account for comprehensive clinical confounders. Ethnic differences in rates of adverse metabolic complications such as hypertension, insulin resistance etc. by BMI (as described above) may begin to explain the observed ethnicity associations with adverse pregnancy outcomes.

An important confounder of ethnicity and pregnancy outcome is antenatal care attendance. Poor antenatal attendance is associated with a higher risk of adverse pregnancy outcomes (Blondel, Dutilh, Delour, & Uzan, 1993), partially due to undetected and therefore unmanaged complications (e.g. hypertensive disease or GDM) but also due to demographic associations. Women with poor antenatal attendance are more likely to be younger, of low socioeconomic status and education, unmarried, higher parity and have an unplanned pregnancy (Alderliesten et al., 2007; Kramer, 1987; Kupek, Petrou, Vause, & Maresh, 2002; Rowe & Garcia, 2003). Poor antenatal care is also more common among non-European ethnicities, particularly when there are also language barriers to care (Alderliesten et al., 2007; Kupek et al., 2002). In NZ, a significant proportion of Pacific women book late in pregnancy and have poor antenatal care attendance (P. Low et al., 2005). Factors that are associated with late booking and poor antenatal

care among Pacific women are consistent with international reports and include nulliparity, high parity and lack of employment.

4.4.1. Ethnicity and birthweight

Ethnicity has an association with infant birthweight that is independent of maternal height, weight and other pathological pregnancy features (Chung, Boscardin, Garite, Lagrew, & Porto, 2003; Drooger et al., 2005; Kelly et al., 2009). It is unclear whether differences in birthweight between ethnicities relate to genetic or heritable factors, or possibly unknown cultural and/or lifestyle differences (see also Chapter 5).

Traditionally, studies into ethnic differences in birthweight have been limited by not being able to include maternal height and weight data. Occasionally, acknowledgement of differences in birthweight between ethnicities has resulted in the creation of separate population birthweight references for some ethnicities, which inherently adjust for mean differences in height and weight (and parity) between ethnicities, however these references are not in widespread use (G. R. Alexander, Kogan, & Himes, 1999; L.M.E. McCowan & Stewart, 2004; J. Zhang & Bowes, 1995). Studies using population birthweight references, typically created from European births, describe high rates of SGA infants among various ethnic groups, including Asian, Indian, African, Hispanic and Māori ethnicities (G. R. Alexander, Wingate, Mor, & Boulet, 2007; Kramer, 1987; Lang, Cohen, & Lieberman, 1992; Mantell, Craig, Stewart, Ekeroma, & Mitchell, 2004; Thompson et al., 2001). As these studies only account for limited confounding factors and rarely adjust for maternal height and weight, much of the difference between ethnicities could potentially be accounted for by these pathological and physiological characteristics. However studies that are able to adjust for some of these factors still show small ethnic differences in rates of SGA (Thompson et al., 2001).

In NZ, mean term birthweights vary considerably between ethnicities, with Tongan and Samoan infants significantly heavier and Indian infants significantly lighter at term than infants from all other ethnic groups including European (L.M.E. McCowan & Stewart, 2004). As described above, these population birthweights are confounded by both maternal characteristics and ethnicity; for example Tongan women are on average taller and heavier than Indian women (National Women's Health, 2012). The associations between maternal height, weight and ethnicity are evidenced by a NZ study that investigated risk factors for SGApop (Thompson et al., 2001). On univariable analysis strong ethnic associations with SGApop were observed, with Pacific ethnicity protective of SGApop (OR 0.72, 95% CI 0.55–0.95), while Indian ethnicity had a substantial increased odds (OR 4.36, 95% CI 2.86–6.64) compared with European. Subsequent multivariable analysis that included maternal height and weight as well as other demographic characteristics, accounted for the association between Pacific ethnicity and SGApop (aOR 0.75, 95% CI 0.51–1.09) however Indian ethnicity still remained a significant risk factor (aOR 3.22,

95% CI 1.95–5.30). Internationally, Indian infants consistently have some of the lowest average birthweights (Kandraju et al., 2012; Mikolajczyk et al., 2011; Nanayakkara, Samarakoon, Perera, De Silva, & Nanayakkara, 2011), with rates of SGA approaching 30% when using European birthweight references (Kramer, 1987) or 60% when using an intrauterine ultrasound reference developed from a European cohort (Mikolajczyk et al., 2011). Clearly these references over-estimate growth restriction in these non-European ethnicities. Even after accounting for gestational age, maternal height and weight and pathological factors, South Asian ethnicities are independently associated with a decrease in birthweight compared with European ethnicity (Gardosi & Francis, 2009b; Loetscher, Selvin, Zimmermann, & Abrams, 2007; Makgoba et al., 2012). By using a population birthweight reference derived from European births, Thompson and colleagues are likely to have overestimated the risk for SGApop in Indian mothers. Their study did however have the advantage of including maternal height and weight data which accounted for some of the ethnic differences initially observed on univariable analysis. As previously mentioned, particular caution must be used in interpreting birthweight studies that don't account for maternal height and weight as this will further overestimate SGApop rates in women who are of smaller stature and underestimate SGApop rates in women of larger stature (see also sections 3.4.1.2 above and 5.2 below).

It is important to note that debate remains as to whether the difference in birthweight between ethnicities are physiological or pathological. Once maternal stature and pathological influences on birthweight are accounted for, it has been argued that differences in birthweight between ethnicities may also explain observed differences in adverse perinatal outcome. Kramer and colleagues have suggested that lower birthweights in black American infants reflects pathology not physiology, where SGApop rates using a European-based standard better identified infants at-risk of perinatal mortality than an ethnicity-specific SGApop reference (Kramer, Ananth, Platt, & Joseph, 2006). In addition, Kelly and colleagues have suggested that differences in birthweight in some ethnicities can be accounted for by differences in socioeconomic or behavioural factors (e.g. smoking) suggesting a pathological basis for these differences (Kelly et al., 2009). In contrast, Kierans and colleagues found that despite lower birthweights, infants of South Asian and Chinese mothers had lower perinatal mortality risks compared with infants of other ethnicities, and ethnicity-specific population birthweight standards better identified infants at-risk of perinatal mortality (Kierans et al., 2008). They suggest that ethnic differences in fetal growth are more likely to be physiological rather than pathological. None of these studies were able to account for pathological clinical factors associated with fetal growth restriction such as hypertensive disease etc. Studies of SGA that include adjustment for pathological factors as well as ethnicity are commonly evaluating customised birthweight references. Infants who are SGApop but are reclassified as non-SGA by customised birthweight centiles (non-SGAcust, see

also Chapter 5) have no or negligible increased risk of perinatal death compared with non-SGA infants by both classifications (Clausson, Gardosi, Francis, & Cnattingius, 2001; Gardosi, Clausson, & Francis, 2007; L. M. E. McCowan, Harding, & Stewart, 2005; J. Zhang et al., 2010; X. Zhang, R. W. Platt, et al., 2007). Although the ethnicity component of the customised birthweight has not been analysed separate to the other included maternal characteristics (height, weight and parity), the overall effect suggests these infants are more likely to be constitutionally rather than pathologically small.

Ethnicity-associated impacts on birthweight could relate to heritable traits (genetic or epigenetic) or cultural factors that are not generally included in retrospective multivariable analyses such as diet and exercise during pregnancy (Gatrad, Ray, & Sheikh, 2004; Liamputtong, Yimyam, Parisunyakul, Baosoung, & Sansiriphun, 2005). Equally, differences may relate to factors related to health inequalities; for example Māori and Pacific peoples are more likely to have poor food security (lack of access to nutritionally adequate and safe foods) and associated poor nutrition (University of Otago and Ministry of Health, 2011). Differences observed in health outcomes because of poor nutrition (including in pregnancy) may then have an ethnic association, but are caused by environmental rather than specific cultural or genetic traits.

4.4.2. Ethnicity and pre-eclampsia

As with birthweight, differing rates of pre-eclampsia have been reported between ethnicities, but confounders such as BMI are rarely included in analyses. Compared with European women, increased rates of hypertensive disorders including pre-eclampsia are observed among African-American, Hispanic/Latina and Filipino women (Irwin, Savitz, Hertz-Picciotto, & St Andre, 1994; Myatt et al., 2012; Rao, Cheng, & Caughey, 2006; Rao, Daniels, et al., 2006; Tanaka et al., 2007) while consistently reduced rates are observed among Chinese women (Caughey et al., 2005; Leung et al., 2008; Rao, Cheng, et al., 2006).

In NZ few data exist on ethnic differences in hypertensive diseases of pregnancy. A single study performed 15 years ago reported no increase in risk of hypertensive disorders of pregnancy among Māori women compared with European, and an increased risk of hypertensive disorders of pregnancy in Pacific women which disappeared on adjustment for maternal BMI, however no other confounding factors were adjusted for (Stone et al., 1995). Unadjusted data from NWH suggest that pre-eclampsia is more common among Māori and Pacific women, with a possible reduced rate among Asian women (National Women's Health, 2012). Modern data regarding pre-eclampsia risk among NZ ethnicities, adjusted for important clinical confounders of ethnicity and pre-eclampsia, are lacking and an analysis of ethnicity-related risk of pre-eclampsia in a NZ cohort is presented in Chapter 9.

Reasons for observed differences in rates of pre-eclampsia between ethnicities are unclear, but are likely to involve confounding factors that have not been accounted for in previous analyses,

most importantly BMI. Other pre-eclampsia confounding factors that may have ethnicity associations include cultural factors such as; duration of sexual relationship, time to conceive, use of barrier contraception, alcohol consumption, cigarette smoking and diet (Dekker, 1999; North et al., 2011; Sibai et al., 2005; Tam et al., 2011). Diets that are high in fruits, vegetables, and fish have been reported to have protective associations with pre-eclampsia, while those with a high intake of processed foods may have an increased risk of pre-eclampsia (Meltzer et al., 2011; North et al., 2011). Although food choices have a cultural component, they are also related to socioeconomic status, with poverty associated with food insecurity leading to a poor diet lacking in fruit and vegetables (University of Otago and Ministry of Health, 2011). Low socioeconomic status can also be a source of stress, and stress may also be linked to an increased risk of pre-eclampsia (Klonoff-Cohen, Cross, & Pieper, 1996; Landsbergis & Hatch, 1996; Marcoux, Berube, Brisson, & Mondor, 1999; Vollebregt et al., 2008).

Bodnar and colleagues have also described an interesting seasonal variation in rates of pre-eclampsia among European women that was not present in African American women in the USA (Bodnar, Catov, & Roberts, 2007). European women had lower rates of pre-eclampsia in the summer months, suggesting the possibility that environmental factors may have a variable impact on ethnic groups with regard to risk of pre-eclampsia. Seasonal environmental factors could include differences in physical activity, diet, infections, depression, anxiety and sunlight, all of which could potentially influence pre-eclampsia risk (Bodnar, Catov, & Roberts, 2007). For example, sunlight during the summer months may increase vitamin D levels among women with lighter skin pigments but not in women with darker skin pigments, where low vitamin D has been associated with increased rates of pre-eclampsia (Meltzer et al., 2011; C. J. Robinson, Alanis, Wagner, Hollis, & Johnson, 2010).

The possibility of a genetic/ heritable component to risk of pre-eclampsia (including epigenetic mechanisms) is suggested by the association between family history of pre-eclampsia or coronary heart disease and pre-eclampsia. Studies have investigated various biomarkers and genes, including between ethnic groups, looking for predictors or associations with pre-eclampsia although none have provided clinically robust findings (Mistry et al., 2011; Ozturk, Balat, Pehlivan, Ugur, & Sever, 2011; Seed et al., 2011; Than et al., 2011; Thomas et al., 2001). If reliable biomarkers/ genetic factors are discovered, an ethnicity-based association with pre-eclampsia may be proven.

4.4.3. Ethnicity and Caesarean section

Ethnic differences in CS rates have been observed internationally, with elevated CS rates observed in African, Filipino, Hispanic/Latina, South Asian/Indian and South American women (Bryant, Washington, Kuppermann, Cheng, & Caughey, 2009; Chung et al., 2006; Getahun et al., 2009; Ibison, 2005; E. B. Johnson, Reed, Hitti, & Batra, 2005; Thomas et al., 2001; Vangen,

Stoltenberg, Skrondal, Magnus, & Stray-Pedersen, 2000; Vangen, Stray-Pedersen, Skrondal, Magnus, & Stoltenberg, 2003), but also decreased CS rates in Middle Eastern, Bangladeshi/ Pakistani and Chinese women when compared with European (Shah et al., 2011; Thomas et al., 2001; Vangen et al., 2000). Again, few studies adjust for BMI despite the well-known association between obesity and CS and differences in rates of obesity between ethnicities (see also section 3.4.3 above). CS rates also differ internationally due to local obstetric practice, as evidenced by a Brazilian study that found 54% of their primiparous European women were delivered by CS, with substantially lower CS rates among non-European, particularly indigenous Brazilians (Freitas, Drachler Mde, Leite, & Marshall, 2009). In some countries, much of the differences in CS rates can be attributed to socioeconomic factors including lack of health insurance (Aron, Gordon, DiGiuseppe, Harper, & Rosenthal, 2000; Chung et al., 2006; Freitas et al., 2009), but it has also been highlighted that increased CS rates are not necessarily beneficial, and these ethnic discrepancies may reflect an over-utilisation of Caesarean delivery by some ethnic groups rather than an under-utilisation by others (Freitas et al., 2009; Kabir, Pridjian, Steinmann, Herrera, & Khan, 2005). In Western countries, increased rates of both elective and emergency CS are observed among wealthy women who have private obstetric care (Alves & Sheikh, 2005; Barley et al., 2004; Thomas et al., 2001), which may reflect differences in patient preferences or expectations, differences in obstetric practice, or other non-clinical factors.

There are few NZ studies that have investigated ethnic differences in CS rates. Johnson and colleagues found lower CS rates among Māori and Pacific women compared with European women however a multivariable analysis was not performed (N. P. Johnson, Lewis, & Ansell, 1995). Subsequently, Sadler and colleagues observed at NWH that Māori and Pacific women had lower rates of overall obstetric intervention (Māori aOR, 0.85, 95% CI 0.78–0.93; Pacific aOR 0.69, 95% CI 0.64–0.74) than 'Other' women (non-Māori, non-Pacific) after adjusting for demographic and clinical confounding factors (Sadler et al., 2002). Notably there were no differences in emergency CS rates between ethnic groups after adjustment for confounders. At the time this study was performed, data were not available for BMI or smoking, and obesity prevalence will have been less than currently observed. Consistent with these findings, a further NZ study performed by Harris and colleagues used national data and found an overall increased odds of CS among non-Māori compared to Māori women (adjusted for age and socioeconomic deprivation: aOR 1.43, 95% CI 1.39–1.48). Further adjustment for limited clinical factors (fetal malpresentation, gestation at delivery, multiple birth, hypertension, diabetes and antepartum haemorrhage) was performed for women who did not have a previously documented delivery (presumed nulliparous women) and CS odds among non-Māori remained higher than in Māori women (aOR 1.16, 95% CI 1.10–1.23). As parity is not reported nationally, nulliparity in this study was inferred and was likely to be overestimated as identifying previous births to an

individual is difficult with national statistics. Misclassification of nulliparity is also more likely in Māori women who have, on average, higher parity than European women.

At NWH in 2008, lower rates of CS in Māori and Pacific nulliparous women were observed, even after stratifying for BMI, Figure 4.1 (National Women's Health, 2008). These data include all CS, where elective and emergency CS have differing associated risks and confounders (Alves & Sheikh, 2005; Roman, Blondel, Breart, & Goffinet, 2008), and are also unadjusted for confounders such as age (Māori and Pacific women are younger at their first birth compared with European)(Ministry of Health, 2011; National Women's Health, 2012), induction of labour or other clinical factors. However these ethnic differences in CS rates may also indicate that the World Health Organization (WHO) BMI criteria are not appropriate for defining obesity-related CS risk among all non-European ethnicities. Differences in CS rates between NZ ethnic groups (after adjustment for known clinical confounders) are investigated in Chapter 10.

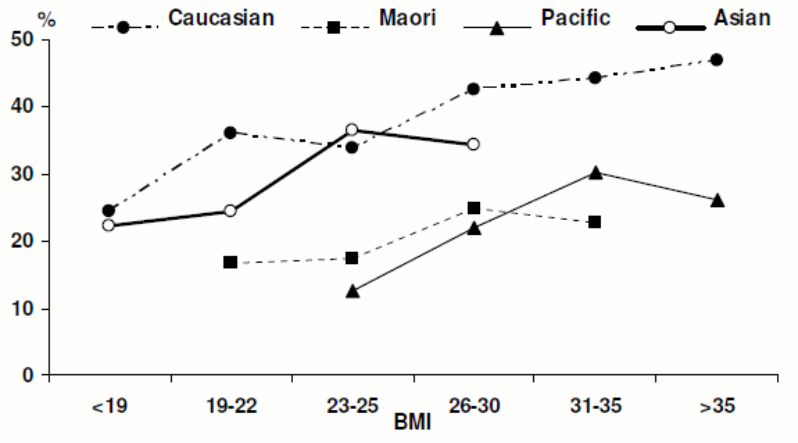


Figure 4.1 Caesarean section rate by BMI and by ethnicity among nulliparous mothers at National Women's Health. Reproduced with permission National Women's Health, 2009.

Decision making around CS is complex and, as mentioned above, there are different clinical and non-clinical factors involved in the decision to undertake elective compared with emergency CS (Roman et al., 2008). There is a clear independent association between affluence, private insurance, private obstetric care and elective CS which reflects non-clinical factors including patient preference or expectations as well as differences in private compared with public obstetric practice (Bragg et al., 2010; Roman et al., 2008; Stavrou et al., 2011; Thomas et al., 2001). Importantly, fear of childbirth, particularly after a previous difficult childbirth experience, is an important reason for patient requested CS (Tschudin et al., 2009; Wax, Cartin, Pinette, & Blackstone, 2004). In contrast, a decision for emergency CS is based on clinical need, however clinical criteria for emergency CS are often not clear-cut and influences such as patient or provider preference may sway a decision for or against CS. Women who have a preference for

CS ultimately have a higher rate of emergency as well as elective CS (Fuglenes, Aas, Botten, Øian, & Kristiansen, 2012).

Many cultures have specific beliefs and traditions that surround pregnancy and childbirth which can substantially influence women's choices and behaviours around labour and birth (Gatrad et al., 2004; Liamputtong et al., 2005; Maimbolwa, Yamba, Diwan, & Ransjo-Arvidson, 2003). Accordingly, the acceptability of CS as a mode of delivery may differ between cultures, meaning that patient requested elective CS may differ by ethnicity. In contrast, rates of emergency CS are less likely to differ between ethnicities after accounting for confounding factors, although there remains the possibility that cultural differences in childbirth expectations (e.g. strong opinions regarding vaginal versus CS delivery) may influence emergency CS rates. Reasons for any independent ethnic differences in CS rates are most likely to be related to non-clinical patient and/ or caregiver factors which may include inequalities in healthcare access or provision. Importantly, if there are true differences in intervention rates relative to adverse outcomes (i.e. low intervention rates with high adverse perinatal outcomes) then this may be evidence of ethnic/ cultural discrimination (Human Rights Commission, 2012).

4.5. The interaction between ethnicity, BMI and adverse pregnancy outcomes

More recently it has been observed that the association between obesity and pregnancy complications seem to differ by ethnicity (Hedderson et al., 2012; Ramos & Caughey, 2005; Steinfeld et al., 2000; Torloni et al., 2012). In a study of adverse pregnancy outcomes among obese women (BMI ≥30), Ramos and colleagues found an increased risk of CS in African American (aOR 1.50, 95% CI 1.04–2.16), Latina (aOR 1.27, 95% CI 1.04–2.16) and Asian women (aOR 1.73, 95% CI 1.13–2.63) compared with European women, along with an increased risk of GDM in Latina (aOR 1.94, 95% CI 1.24–3.03) and Asian women (aOR 2.20, 95% CI 1.38–3.49) and an increased risk of pre-eclampsia among Latina women (aOR 1.93, 95% CI 1.24–3.01) (Ramos & Caughey, 2005). Torloni and colleagues have also described an increased risk of spontaneous preterm birth among obese European women (aOR 1.84, 95% CI 1.15–2.95), but not obese African American women (aOR 0.72, 95% CI 0.38–1.40) (Torloni et al., 2012). Additionally, Hedderson and colleagues observed an increase in risk of GDM in Asian and Filipino women at a lower BMI compared with Hispanic, European and African American women (Hedderson et al., 2012). Importantly, they also calculated the population attributable risk (PAR) of overweight and obesity (BMI ≥ 25kg/m^2) on GDM prevalence (the theoretical decrease in risk of GDM if overweight and obesity was eliminated from a population), and due to the low prevalence of excess adiposity among Asian women and high prevalence among African American women, this PAR estimate ranged from only 23% among Asian women to 65% among African American women. This means that although Asian women have a greater degree of risk

for a lesser degree of adiposity, interventions to decrease pre-pregnancy weight that target African American women would result in a greater overall decrease in GDM prevalence.

A single study has investigated a range of obstetric outcomes by differing BMIs, and this was among Hong Kong Chinese women (Leung et al., 2008). Similar to Hedderson and colleagues, Leung and colleagues observed that odds of adverse pregnancy outcomes such as CS and GDM increased at a lower BMI than described in European populations (23-25kg/m^2), while the overall odds of adverse pregnancy outcomes in women with a BMI ≥30kg/m^2 (such as preterm birth, pre-eclampsia and GDM) were higher in Chinese women when compared with studies performed in European women. These findings mimic those of a previously mentioned analysis in non-pregnant Hong Kong Chinese adults that showed an increased rate of obesity-related complications (i.e. hypertension, diabetes and dyslipidaemia) at lower BMI levels than European (Ko et al., 1999) (see also section 4.3 above). These findings suggest that ethnicity adjusted BMI criteria may better classify adiposity-related pregnancy risk among Chinese women, consistent with the ethnic-specific BMI classification suggested by the WHO (WHO/IASO/IOTF, 2000). There are few studies in Māori or Pacific adults (pregnant or non-pregnant) that have included BMI, and none that have investigated health outcomes by BMI criteria other than WHO criteria. Chapter 7, Chapter 9 and Chapter 10 of this thesis provide analyses of the impact of ethnicity on a range of pregnancy outcomes (SGA, pre-eclampsia and CS) after accounting for BMI.

4.6. Summary

Ethnicity is a complex social concept of self-perceived cultural affiliation. Although there are many factors that contribute to an individual's ethnicity affiliation (and these may change with time and circumstances), people that belong to an ethnic group generally have common characteristics including those related to health. Accurate reporting of ethnicity allows any potential ethnic-inequalities to be identified, and can target research, interventions and policies to address these inequalities. Ethnicity has associations with many adverse health outcomes which are confounded by demographic associations. However, data from Asian and Indian studies suggest that lower BMI criteria for overweight and obesity may better reflect adiposity-related health risks, which is consistent with an increased adiposity at lower BMI levels for these ethnicities.

Limited data on ethnicity in pregnancy show associations with adverse outcomes such as rates of SGA infants, pre-eclampsia and CS, although studies commonly don't include clinical confounders such as BMI. The strength of associations between ethnic groups and adverse pregnancy outcomes vary, and the few studies that include BMI suggest that BMI has a differential impact on adverse pregnancy outcomes observed between ethnicities (which may

relate to differing levels of adiposity or body-fat distribution). Only two studies have investigated adverse outcomes by ethnicity in a range of BMI categories, and suggest lower BMI criteria (such as those reported by the WHO) may be appropriate to define adiposity-related pregnancy risk in Chinese/ Asian women. Minimal data exist on pregnancy outcomes among NZ's ethnic groups, including no studies investigating the appropriateness of ethnic-specific BMI criteria for Māori and Pacific women.

Chapter 5. | Infant birthweight

5.1. Introduction

Infant birthweight is determined by the interaction between intrinsic (genetic) and extrinsic (environmental) influences. Infants who are abnormally grown are more likely to have both immediate and long-term complications associated with exposure to an adverse intrauterine environment, but the challenge is how to define normal and abnormal growth. Research has traditionally focused on identifying FGR over excess fetal growth as growth restriction is associated with a greater increase in perinatal morbidity and mortality, and timely identification and intervention can improve outcomes (Lindqvist & Molin, 2005). Whether perinatal outcomes can be improved with interventions among macrosomic infants identified before birth is less well established (Boulvain et al., 2012; Sanchez-Ramos, Bernstein, & Kaunitz, 2002)(see section 3.4.1 above). As would be expected, the greatest contributor to infant weight is gestational age (Bukowski et al., 2008; Gardosi et al., 1992) however there are multiple other factors that influence birthweight, both physiological and pathological.

5.2. Determinants of fetal growth

Normal fetal growth encompasses a wide range of variability, particularly at term, with only 25-35% of birthweight among infants with normal outcomes predicted by current multivariable regression models (Bukowski et al., 2008; Gardosi & Francis, 2009b). With this amount of normal variability, it follows therefore that physiological fetal growth can be difficult to determine from pathological growth. Physiological determinants of fetal growth are constitutional factors that are associated with normal growth. A fetus that achieves its growth potential can therefore be considered to have a normal interaction between genetic and environmental influences. In contrast, pathological fetal growth occurs when the fetal growth potential is restricted or exceeded due to external influences, resulting in birthweights outside of 'normal' limits and increased rates of adverse perinatal outcomes.

5.2.1. Physiological

Gestational age

The greatest physiological determinant of birthweight is gestational age; as pregnancy progresses the fetus grows. Early in pregnancy, particularly the first trimester, there is less variability in fetal growth between individuals as growth is primarily due to increases in cell number. Fetal adipose, muscle and connective tissue accumulates later in pregnancy (Yu & Upadhyay, 2004), and these components are more strongly influenced by genetic and pathological factors than early growth (Gardosi et al., 1992; Kramer, 1987).

Genetic and maternal contributors

Genetic and constitutional environmental factors make up the remainder of normal fetal growth determinants. Male infants are larger than female infants (on average 120g–150g heavier at term)(Bukowski et al., 2008; Gardosi & Francis, 2009b; Kramer, 1987). In addition, maternal characteristics such as height, pre-pregnancy weight and ethnicity also determine the extent of normal fetal growth. Maternal stature influences fetal growth through both the inheritance of the mother's genetic potential as well as any physical limitations on fetal growth caused by a small maternal stature (maternal constraint) (Kramer, 1987; J. Morrison, Williams, Najman, & Andersen, 1991) The effect of obesity and ethnicity on birthweight have been reviewed above (please see sections 3.4.1 and 4.4.1 above); in summary, increasing pre-pregnancy height and weight are positively associated with birthweight, and ethnicity has an independent influence on birthweight that is likely to be physiological. Obesity is additionally associated with pathological growth; both excess fetal growth and FGR.

Maternal age

Maternal age has been inconsistently associated with birthweight. Older maternal age (>35 years) may be a risk factor for SGA (L.M.E. McCowan & Horgan, 2009; Odibo, Nelson, Stamilio, Sehdev, & Macones, 2006) (see section 5.2.2 below), but increasing maternal age is also associated with increasing birthweight (Pain, Chang, Flenady, & Chan, 2006). The association between maternal age and birthweight is confounded by many associations, e.g. increasing obesity and hypertensive disease with increasing age, but is particularly confounded by parity. Increasing maternal age is inevitably associated with increasing parity, and higher parity is in turn associated with increasing birthweight (Bukowski et al., 2008; Kramer, 1987). The association between maternal age and parity is complex however, as affluent women are increasingly delaying childbearing and are becoming older at the time of first birth (Montan, 2007). Multivariable studies that are able to account for a wide range of clinical variables commonly show no association between maternal age and birthweight (Bukowski et al., 2008; Gardosi, Mongelli, Wilcox, et al., 1995).

Parity

Parity has a well-established association with birthweight (Kramer, 1987), with an independent increase of 100-150g from first to second birth, and lesser increases in birthweight for subsequent births (Bukowski et al., 2008; Catalano, Thomas, Huston, & Fung, 1998; Gardosi, Mongelli, Wilcox, et al., 1995). As with ethnicity, the appropriateness of adjusting for parity, particularly nulliparity, as a physiological determinant of birthweight has been challenged, as first pregnancies are at increased risk of perinatal death and other perinatal morbidities (Bai, Wong, Bauman, & Mohsin, 2002; Battin, McCowan, George-Haddad, & Thompson, 2007; Ego et al., 2008; X. Zhang, S. Cnattingius, et al., 2007). Firstborn children may also be at additional risk

of later metabolic consequences which adds to the suggestion that a lower birthweight among nulliparous women has a pathological component (Gluckman & Hanson, 2004).

Zhang and colleagues performed an indirect comparison of perinatal death rates by gestational age in two SGApop birthweight models; 1. adjusted for a lower expected birthweight in nulliparous women 2. unadjusted for parity (a standard population birthweight reference) (X. Zhang, S. Cnattingius, et al., 2007). They found higher perinatal death rates in nulliparous women at all gestational ages, which were better modelled by rates of SGApop from the unadjusted birthweight reference (model 2 above). This association remained after adjustment for demographic confounding (infant sex, maternal age, marital status, education, smoking and ethnicity). Their study was not able to account for confounding factors such as hypertensive disease or diabetes and, similar to analyses by Gardosi and colleagues, this indirect argument relies on the assumption that SGA rates accurately reflect perinatal death rates among nulliparous women. While SGA is likely to be an important contributor to perinatal death in first-time mothers, other factors are also likely to influence perinatal mortality rates among these women (see also section 3.4.1.2 above). Additionally, although they also concluded that low maternal BMI and short stature were physiologically associated with birthweight, these were not subsequently included in their models. Based on these findings, the lower birthweight observed in nulliparous women could be considered pathological rather than physiological.

In a further study, Ego and colleagues discussed the proposed benefits of not customising for parity in a customised birthweight model, arguing that nulliparous women are at increased clinical risk and it is not clear that the lower birthweights in these women should be normalized as physiological (Ego et al., 2008). They compared two customised centile models differing only in whether parity was included, and found that excluding parity (i.e. assuming birthweight differences due to parity are not physiological) increased the number of nulliparous women identified as having SGA infants (from 14.9% to 18.0%) without any change in the identification of high-risk infants or perinatal mortality. They asserted that the lack of difference in perinatal risk between models both simplifies the customisation procedure and allows for greater numbers of nulliparous women to be identified as SGA, reflecting their overall risk status.

In response, Gardosi and colleagues (in a similar analysis to Ego and colleagues), argued that the exclusion of parity substantially overestimated the rate of SGA among nulliparous women in that it did not reflect the small increase in perinatal death among these women (Model 2, Table 5.1)(Gardosi & Francis, 2009c). Additionally, the exclusion of parity underestimated SGA rates among women with 4+ births as these women also had an increased rate of perinatal death. In contrast, customisation that included parity seemed to result in SGA rates that better reflected perinatal mortality (Model 1, Table 5.1). Again, this indirect comparison relies on the same assumption that SGA rates reflect perinatal death rates between women of differing parity.

Table 5.1. Perinatal mortality and smallness for gestational age (SGA) in models that customise birthweight with and without parity. Reproduced from Gardosi et al., BJOG (2009), Parity and smallness for gestational age (comment), 116 (8) 1135-6. DOI: 10.1111/j.1471-0528.2009.02127.x with permission.

Parity (after birth)	Perinatal mortality (per 1000)	Model 1 SGA customised with parity (%)	Model 2 SGA customised without parity (%)
1	5.6	12.7	17.2
2	4.2	11.6	10.0
3	5.3	12.3	9.4
4+	6.2	14.0	10.6

Similar findings were observed in a further analysis performed by Gardosi and colleagues where perinatal death rates were compared between SGAcust and SGApop infants stratified by parity (in the same way as maternal size was investigated, see section 3.4.1.2 above) (Gardosi et al., 2009). They describe SGApop as overestimating the relationship between nulliparity and perinatal death while underestimating the relationship between multiparity and perinatal death. While there was no difference in statistical significance between the curves of perinatal death by parity for either SGA definition (perinatal death versus SGAcust: P = 0.778; perinatal death versus SGApop: P = 0.160), adjustment for parity appeared to better reflect rates of perinatal

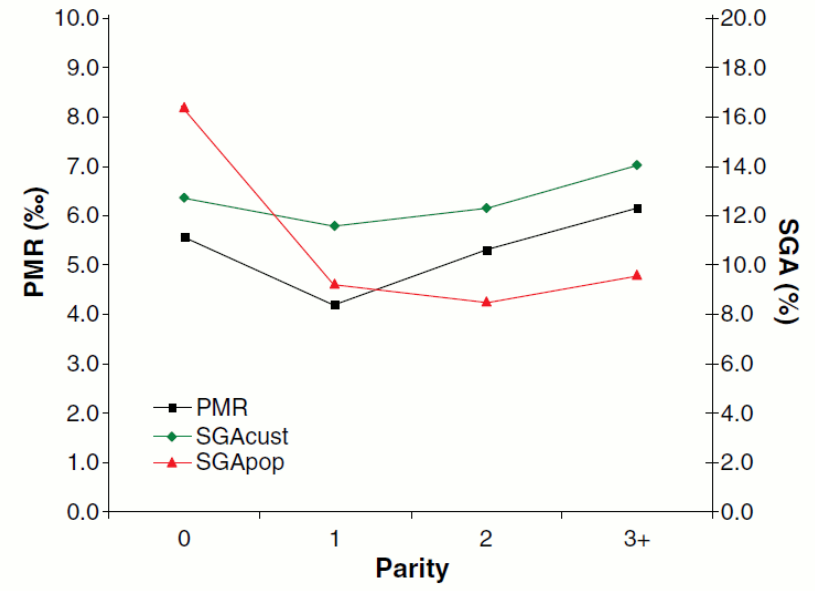


Figure 5.1 Perinatal mortality rate (PMR) and smallness for gestational age (SGA) by customised (SGAcust) and population-based centiles (SGApop), according to maternal parity at the beginning of pregnancy. *t*-test for difference of slopes: PMR versus SGAcust: *P* = 0.778; PMR versus SGApop: *P* = 0.160. Reproduced from Gardosi et al., BJOG (2009), The value of customised centiles in assessing perinatal mortality risk associated with parity and maternal size, 116 (10) 1356-1363. DOI: 10.1111/j.1471-0528.2009.02245.x with permission.

death, particularly among nulliparous women, Figure 5.1 (Gardosi et al., 2005). With the previously discussed assumption of SGA rates reflecting perinatal death rates among women of differing parity in mind, these indirect findings support the adjustment for parity in customised birthweight models, and suggest that despite the increased clinical risk associated with nulliparity an adjustment of birthweight for parity better reflects SGA-related perinatal death. Therefore birthweight differences by parity can be considered physiological.

Paternal contributors

In contrast to maternal characteristics, paternal characteristics have a smaller contribution to fetal growth (Kramer, 1987; J. Morrison et al., 1991; Wilcox, Newton, & Johnson, 1995). This differential influence on the fetus is expected based on cross-breeding studies performed in other mammals, particularly the classic studies of Walton and Hammond where Shetland ponies and Shire horses were interbred, with the resulting foals a similar size to maternal pure-bred foals (Catalano et al., 1998; Walton & Hammond, 1938). Although the contribution is small, paternal height and weight still have significant associations with infant birthweight, however this association is confounded by correlations between maternal and paternal size (assortive mating; where couples tend to choose a partner of a similar stature) (Kramer, 1987; Wilcox et al., 1995). In the case of discrepancies in maternal and paternal characteristics, infant birthweight is particularly correlated with paternal height (J. Morrison et al., 1991; Wilcox et al., 1995) with an approximate 150–180g increase in term birthweight for tall fathers, dependent on maternal size (J. Morrison et al., 1991; Wilcox et al., 1995).

More recent associations have been described between paternal SGA at birth and an increased risk of SGA in their offspring (Jaquet et al., 2005). This suggests a specific paternal genetic or epigenetic contribution to SGA. Additionally, an independent association has also been observed between paternal obesity and central adiposity with birth of an SGA infant (L. M. E. McCowan et al., 2011) (see also section 5.2.2 below). The reasons for this association remain unclear, but may include environmental factors i.e. shared dietary and/or physical activity habits between the couple, paternal genetics or a combination of both (L. M. E. McCowan et al., 2011).

5.2.2. Pathological

Pathological influences on fetal growth are usually manifested as birthweights that are outside the limits of normal variability. Pathological processes result in an intrauterine environment that places stress on the fetus, and as a result the growth potential of the fetus is either not achieved (FGR) or is exceeded (macrosomia), resulting in adverse perinatal and long-term outcomes for the infant. As previously discussed, excess fetal growth is associated with excess fuel substrates for growth, i.e. maternal obesity and diabetes (see also section 3.4.1.1 above) and other than rare genetic disorders these common pathological factors are the only currently known associations with macrosomia. The rest of this review will focus on inadequate fetal

growth. For the purposes of completeness, in addition to those risk factors described below FGR is also associated with chromosomal abnormalities such as trisomies or monosomies, as well as with major fetal abnormalities (Snijders, Sherrod, Gosden, & Nicolaides, 1993), however these infants are not the focus of this body of work and will not be considered further.

Inadequate fetal growth is difficult to both identify and define. With normal fetal growth having a large amount of variability, a fetus may be growth restricted but still lie within 'normal' limits of growth (Stratton, Scanaill, Stuart, & Turner, 1995). Strategies to identify these 'normal weight, growth restricted' infants include serial antenatal monitoring of fetal growth (fundal height measurements or serial ultrasound biometry) and ultrasound measures of uterine and fetal blood flow (Baschat, 2003; Figueras & Gardosi, 2011; Gardosi, 2011). However the infants who are at greatest risk of severe morbidity and mortality are those who comprise the lowest percentages of weight for gestational age, i.e. who are also SGA infants. As previously mentioned, the definition of SGA has traditionally been a birthweight <10th centile for gestational age (Alberry & Soothill, 2007; Thompson et al., 2001; J. Zhang et al., 2010) (see also section 3.4.1.2 above). This cut-off, like others in medicine e.g. blood pressure, lies on a continuum of risk, and it is important to note that those infants that lie just above the 10th centile have a similar risk of adverse outcomes to those just below the 10th centile. Additionally birthweight, like most biological systems, has a normal distribution meaning that some infants classified as SGA are normally grown, and these babies will have a normal outcome.

Although FGR and SGA are not synonymous, risk factor studies have generally investigated SGA pregnancies as a surrogate for FGR, due to the difficulty of defining growth restriction. The use of population birthweight references in these SGA studies may also lead to over- or under-estimation of risk in some groups (see also section 4.4.1 above). However as there is substantial overlap (>70%) between infants that are SGApop and SGAcust (as very small infants are identified by both standards) there will also be overlap of risk factors for SGApop and SGAcust (Gardosi, 2004; Gardosi & Francis, 2009a; L. M. E. McCowan et al., 2005). SGA risk factors identified in observational literature can be considered under the broad categories of; demographic and psychosocial, past obstetric history, toxic exposures, nutrition, maternal medical conditions and pregnancy complications.

Demographic and psychosocial

Women of advanced maternal age (defined variably as >35 years or >40 years) may have an independently increased risk of SGA. As previously mentioned, increasing maternal age is generally associated with increasing parity, but there are also many other confounders of maternal age including increasing obesity, background hypertensive disease as well as an increased risk of gestational hypertensive disease, and gestational diabetes (Montan, 2007; Odibo et al., 2006). Once these confounders are accounted for, some researchers still find an

independent association between advanced maternal age and SGA (Kleijer, Dekker, & Heard, 2005; Kramer et al., 1999; Meis et al., 1995; Odibo et al., 2006), while others find no association (Lang et al., 1992; Spinillo et al., 1994).

Unadjusted rates of SGA are consistently elevated among socioeconomically deprived women however poverty also has many confounders of birthweight such as increased rates of cigarette smoking, obesity as well as ethnic associations. Multivariable analyses that account for these confounders are conflicting, with some studies showing no independent association between socioeconomic status and SGA (Kramer, 1987; Thompson et al., 2001), while others have found significant correlations (Raum, Arabin, Schlaud, Walter, & Schwartz, 2001; Wilcox et al., 1995).

Psychosocial stress (including anxiety and depression) also has conflicting associations with SGA. Again, stress has many confounders including poverty, however some researchers have found self-reported stress to be linked with increased rates of SGA (Paarlberg et al., 1999). Surrogates for anxiety and depression such as domestic violence and mental illness have also been associated with an increased risk of SGA (Kleijer et al., 2005), while other multivariable studies have found no association between stress and SGA (Kramer, 1987; Pryor et al., 2003). Consistent with this contradictory data, women with depression have been reported to both be at additional risk (Bonari et al., 2004), and at no increased risk of SGA (Andersson, Sundstrom-Poromaa, Wulff, Astrom, & Bixo, 2004).

Low maternal birthweight has been found to be a risk factor for SGA (Jaquet et al., 2005; Magnus, Bakketeig, & Skjaerven, 1993; L.M.E. McCowan et al., 2010), with mothers who were themselves SGA at birth having a greater than four-fold increase in odds of an SGA infant (aOR 4.70, 95% CI 2.36–9.38) (Jaquet et al., 2005). This same study also estimated a greater than three-fold increase in odds of SGA with fathers who were SGA (aOR 3.47, 95% CI 1.17–10.27) suggesting that paternal genetic or heritable factors are likely to contribute to the risk of infant SGA.

Past obstetric history

Past obstetric history is a strong predictor of current pregnancy risk. Women with previous stillbirth or SGA have shown they have the potential to develop an adverse intrauterine environment for a fetus, and as such have a greater chance of SGA in a future pregnancy (Bakewell, Stockbauer, & Schramm, 1997; Heinonen & Kirkinen, 2000; Kleijer et al., 2005; Kramer, 1987). Women with a previous SGA infant also have an increased chance of stillbirth in a subsequent pregnancy, with increasing risk proportional to the degree of growth restriction and prematurity of the previous infant (G. C. Smith, Shah, White, Pell, & Dobbie, 2007; Surkan et al., 2004). The risk of recurrence of SGA in a subsequent pregnancy is compounded by a short inter-pregnancy interval, where the optimum duration between pregnancies is 18–23 months (Conde-Agudelo, Rosas-Bermudez, & Kafury-Goeta, 2006). Women with an inter-pregnancy

interval less than this have higher rates of SGA, with the greatest risk occurring with a duration between pregnancies of <6months (aOR 1.26, 95% CI 1.18–1.33).

Both prior miscarriage and infertility may be risk factors for SGA. Women with one or more previous miscarriage have been found in some studies to have an increased chance of SGA (Basso, Olsen, & Christensen, 1998; Spinillo et al., 1994), although not in others (Lang, Lieberman, & Cohen, 1996), while infertility has been observed as a risk factor for SGA, both with and without fertility treatment (Basso & Baird, 2003; Camarano et al., 2012; Helmerhorst, Perquin, Donker, & Keirse, 2004; L.M.E. McCowan et al., 2010; J. L. Zhu, Obel, Hammer Bech, Olsen, & Basso, 2007).

Toxic exposures

In the context of birthweight, toxins can be considered environmental exposures that affect fetal growth. The toxins that have the greatest impact on fetal growth in a general obstetric population are those contained in cigarette smoke, where smoking has been attributed as the single most important cause of SGA in many countries (Ashmead, 2003; Cnattingius, 2004; Kramer, 1987; Thompson et al., 2001). This exposure is particularly important as it is also one of the few modifiable risk factors for SGA in pregnancy. A recent prospective study of healthy nulliparous women found those who stopped smoking prior to 15 weeks of gestation had the same risk of SGA (and spontaneous preterm birth) as non-smokers (L.M.E. McCowan et al., 2009). Recent studies on smoking among obese women have also shown that the negative effect of smoking on birthweight is substantially reduced in the presence of maternal obesity (La Merrill, Stein, Landrigan, Engel, & Savitz, 2011), possibly reflecting the competing influences on birthweight among these infants. It is important to consider again the varying smoking rates between ethnicities, with the highest rates of smoking occurring in young NZ women (aged 15-19 years), that range from 50% among Māori to 5% among Asian, compared with 20% of European/Other women (Ministry of Health, 2009b; The Quit Group and the Ministry of Health, 2009).

Other toxin exposures in pregnancy that may impact on fetal growth include caffeine/ coffee, alcohol, marijuana and other illicit drugs. There is conflicting evidence on the role of caffeine in fetal growth. A large prospective observational study showed that a caffeine intake of >200mg/d (one cup of coffee is approximately 100mg) resulted in a 50% increase in odds of SGA (aOR 1.5, 95%CI 1.1–2.1; SGA defined using customised birthweight) (Care Study Group, 2008). In contrast a randomised study showed no differences in birthweight between those who drank caffeinated versus non caffeinated beverages (Bech, Obel, Henriksen, & Olsen, 2007), and a further study that measured a caffeine metabolite in third trimester maternal serum found an association between increased caffeine intake and SGA, but only among cigarette smokers (Klebanoff, Levine, Clemens, & Wilkins, 2002). Overall it is difficult to provide recommendations

for caffeine intake in pregnancy, but cautious moderation of intake is probably advisable. Heavy consumption of alcohol has been associated with an increased risk of SGA (as well as other infant comorbidities such as fetal alcohol syndrome and preterm birth, (Jaddoe et al., 2007)) while low to moderate consumption has not been associated with increased risk; although there is insufficient evidence to suggest alcohol in pregnancy is safe (Henderson, Gray, & Brocklehurst, 2007). Few data exist on the risk of illicit drugs on fetal growth, although once confounding factors are taken into account there have been no consistent associations observed between marijuana and opiates and SGA (Bada et al., 2005; Fergusson, Horwood, Northstone, & ALSPAC Study Team, 2002; Schempf & Strobino, 2008). Cocaine use in pregnancy however has been shown to have an association with SGA that is independent of the social and psychosocial factors that confound illicit drug use (Bada et al., 2005; Schempf & Strobino, 2008).

Nutrition

Traditionally, underweight (BMI <18.5kg/m^2) has been considered a risk factor for SGA by population centiles (Kramer, 1987; Kramer et al., 1999; Lang et al., 1996; Thompson et al., 2001). However, after adjusting for maternal height and weight in customised birthweight centiles, rates of SGAcust among underweight women are reduced when compared with SGApop which corresponds with a decreased rate of perinatal death which also occurs among underweight women (see also section 3.4.1.2 and Figure 3.8 above)(Gardosi et al., 2009). Some of the decrease in perinatal death in thin women may also relate to better identification of SGA (M. Williams et al., 2010). While obesity has also been proposed as a risk factor for SGA it is more difficult to identify among obese women (M. Williams et al., 2010).

In addition to BMI, inadequate GWG has been proposed as a further risk factor for SGA. As previously mentioned in section 3.4.4, low GWG and gestational weight loss have been associated with increased rates of SGA, although it remains unclear whether SGA is the cause of low GWG or low GWG causes SGA. A correlate of the importance of nutrition in pregnancy are seen with women with hyperemesis gravidarum which can lead to severe nutritional deficiencies in early pregnancy. These women have been found to have lower birthweight infants and an increased chance of SGA than those without hyperemesis, particularly if overall GWG was low (Bailit, 2005; Dodds, Fell, Joseph, Allen, & Butler, 2006; Veenendaal, van Abeelen, Painter, van der Post, & Roseboom, 2011).

Specific dietary components have been associated with an increase or decrease in birthweight and/ or risk of SGA. A diet high in green leafy vegetables and fruit has been independently associated with decreased risk of SGA (L.M.E. McCowan et al., 2010; Mikkelsen, Osler, Orozova-Bekkevold, Knudsen, & Olsen, 2006; Mitchell et al., 2004). Fruit and vegetables provide folic acid, iron, vitamins, carotenoids, antioxidants etc. that all may facilitate fetal growth. Milk intake has also been associated with small increases in birthweight (Olsen et al., 2007), while fish

consumption has had variable associations, with both increases (Olsen, Olsen, & Frische, 1990; Rogers, Emmett, Ness, & Golding, 2004) and decreases in fetal growth observed (Halldorsson, Meltzer, Thorsdottir, Knudsen, & Olsen, 2007; Oken, Kleinman, Olsen, Rich-Edwards, & Gillman, 2004). It has been speculated that differences in outcomes between studies of dietary fish intake may relate to the proportion of fatty fish that are consumed, where fatty fish in some geographic regions is associated with exposure to organic pollutants (Halldorsson et al., 2007). Studies into dietary components and fetal weight are predominantly retrospective and observational, meaning associations may also be confounded by unknown other demographic or lifestyle factors.

Due to the observed association between dietary components and fetal growth, dietary supplements have also been investigated to assess any contribution to birthweight. A systematic review of multiple-micronutrient supplementation in pregnancy performed in 2006, found that supplementation resulted in a statistically significant decrease in the number of SGA infants, however this association was lost when compared with folic acid and iron supplementation alone (Haider & Bhutta, 2006). Subsequent studies have suggested small decreases in risk of SGA among women who take low dose multivitamins (Catov, Bodnar, Ness, Markovic, & Roberts, 2007; Poston et al., 2006).

Maternal medical disease

Many maternal medical conditions have well established associations with SGA, particularly those that have underlying endothelial dysfunction as outlined in section 3.4.2 above. Chronic hypertension, which is associated with an increased risk of both pre-eclampsia and SGA, is a relatively common maternal co-morbidity with a prevalence ranging from 0.5-3% depending on the population (Allen, Joseph, Murphy, Magee, & Ohlsson, 2004; L.M.E. McCowan et al., 2010; National Women's Health, 2012; Zetterstrom, Lindeberg, Haglund, & Hanson, 2006). Pre-eclampsia superimposed on chronic hypertension results in an even greater risk of SGA, with an estimated 3-fold increase in odds of SGA among women with chronic hypertension (OR 2.9, 95% CI 1.6–5.0) increasing to an estimated 5-fold increase in odds among women with super-imposed pre-eclampsia (OR 5.6, 95% CI 1.8–16) (L.M.E. McCowan, Buist, North, & Gamble, 1996).

Maternal renal disease is associated with SGA, where the degree of growth restriction is proportional to the degree of renal impairment (Ramin, Vidaeff, Yeomans, & Gilstrap, 2006). An increased risk of SGA is also observed among women with diabetic vasculopathy, independent of renal function (Haeri, Khoury, Kovilam, & Miodovnik, 2008; Howarth, Gazis, & James, 2007). Autoimmune diseases (particularly antiphospholipid syndrome and systemic lupus erythematosus) (Empson, Lassere, Craig, & Scott, 2005; Yasmeen, Wilkins, Field, Sheikh, & Gilbert, 2001) and severe maternal cardiac disease (associated cyanosis and pulmonary

hypertension) are also recognised risk factors for SGA. These maternal diseases all have endothelial dysfunction as an important pathogenic process. Importantly, although these maternal medical conditions have potentially large impacts on fetal growth, with the exception of chronic hypertension they are also uncommon among obstetric populations.

Pregnancy complications

Complications in pregnancy that are associated with SGA are generally indicators of placental dysfunction. These complications include gestational hypertensive disorders and bleeding in pregnancy. The common aetiologies of hypertensive disorders of pregnancy and SGA have been discussed in section 3.4.2 above. In summary, hypertensive diseases and SGA have a shared pathophysiology of endothelial dysfunction and poor placentation, with the degree of maternal disease (hypertension and/ or pre-eclampsia) related to the degree of endothelial dysfunction, which in turn is likely to be associated with maternal predisposing factors. As discussed, there is also no consistent relationship between the severity of hypertensive disease and degree of SGA.

Bleeding in pregnancy can also be considered a marker of placental dysfunction, as a normally implanted placenta does not separate to cause bleeding. Bleeding in early pregnancy (vaginal bleeding or subchorionic haematoma on ultrasound) is common, complicating up to 20% of all pregnancies. Women with heavy vaginal bleeding or evidence of subchorionic haematoma on ultrasound seem to be at increased risk of SGA (Nagy, Bush, Stone, Lapinski, & Gardo, 2003; Weiss et al., 2004). Antepartum haemorrhage (APH), defined as bleeding at or beyond 20 weeks of gestation, has associations with SGA that include both placental abruption (the premature separation of a normally sited placenta, proven by visualisation of retroplacental clot at delivery or on ultrasound (Neilson, 2003)) and antepartum haemorrhage of unknown origin (an unexplained APH after excluding known causes such as lower genital tract bleeding, placenta praevia, vasa praevia and abruption). Abruption, which is more common among women with hypertensive diseases, is consistently and independently associated with an increase in SGA (Ananth, Berkowitz, Savitz, & Lapinski, 1999; Kramer, Usher, Pollack, Boyd, & Usher, 1997; Nath, Ananth, DeMarco, Vintzileos, & for the New Jersey-Placental Abruption Study Investigators, 2008). The degree of SGA has been observed to be greater among abruption that occurs preterm, suggesting greater placental dysfunction. APH of unknown origin may originate from the placenta, and has been inconsistently reported to result in small decreases in birthweight (McCormack et al., 2008) with an increase in risk of SGA (Koifman et al., 2008), although others have found no increase in SGA rates (Chan & To, 1999). Placenta praevia (an abnormally located placenta that abuts or covers the internal cervical os) has previously been considered a risk factor for low birthweight, however recent analyses have shown that this association is mostly due to an increase in preterm birth, and overall placenta praevia has small association with SGA that is of questionable clinical significance (Ananth, Demissie, Smulian, & Vintzileos, 2001).

As previously mentioned, the large majority of the publications cited above have used a population birthweight standard to define SGA. Only one study has investigated risk factors for SGA by customised birthweight, but this was in healthy nulliparous women (L.M.E. McCowan et al., 2010). A formal assessment of clinical risk factors for SGAcust in a general obstetric population has not previously been performed, and this is addressed in Chapter 7.

5.3. Customised birthweight centiles

Customised birthweight centiles have been created in an attempt to better account for normal physiological influences on birthweight. Population references by definition include all births, which also means pregnancies with pathologic conditions that affect fetal growth are included resulting in a flawed assessment of 'normal' growth (Bukowski et al., 2008). In addition, although based on large populations of births, most birthweight references in use in Western countries were created in the 1990's or earlier using predominantly European births, when obesity was not as common (G. R. Alexander, Himes, Kaufman, Mor, & Kogan, 1996; Beeby, Bhutap, & Taylor, 1996; Thompson, Mitchell, & Borman, 1994). The well-established association between preterm birth and fetal growth restriction also means that birthweight references are systematically biased towards lower weights at preterm gestations (Gardosi, 2005; Zeitlin, Ancel, Saurel-Cubizolles, & Papiernik, 2000). To overcome this preterm birthweight bias, population ultrasound-based intrauterine fetal growth references have also been created to define normal growth. These references are based on ultrasound estimations of fetal weight in normal ongoing pregnancies that result in healthy, term births (Hadlock, Harrist, & Martinez-Poyer, 1991; Morken, Kallen, & Jacobsson, 2006). When comparing ultrasound references to birthweight references, the bias of preterm birthweight and SGA becomes obvious, Figure 5.2.

In addition to using an ultrasound-based reference, customised birthweight references also account for maternal and fetal characteristics that have physiological influences on birthweight as discussed above (i.e. maternal height, weight, parity, ethnicity and fetal sex), and exclude pathological influences on birthweight by using a term cohort of births without pathology as the birthweight reference (Bukowski et al., 2008; Gardosi, Mongelli, Wilcox, et al., 1995). Infants who are SGAcust alone (i.e. not SGApop) have consistently been shown to have an increased risk of perinatal mortality and morbidity compared with infants that are SGApop alone (i.e. not SGAcust, Figure 5.3), suggesting that customisation better differentiates between physiological and pathological smallness (Clausson et al., 2001; Figueras et al., 2007; Gardosi & Francis, 2009b; L. M. E. McCowan et al., 2005; Odibo et al., 2010).

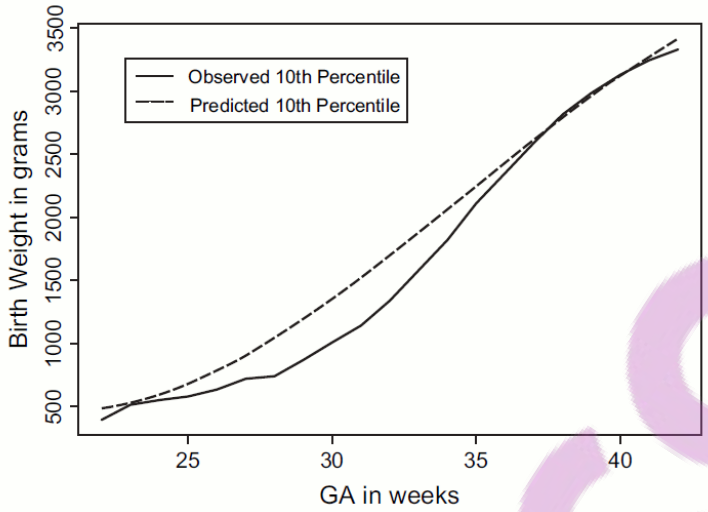


Figure 5.2. Observed and predicted (by an ultrasound fetal weight reference) birthweight 10th percentiles for gestational age. Reprinted from Zhang et al. BJOG (2007), The use of customised versus population-based birthweight standards in predicting perinatal mortality 114 (4) 474-7. DOI: 10.1111/j.1471-0528.2007.01273.x with permission.

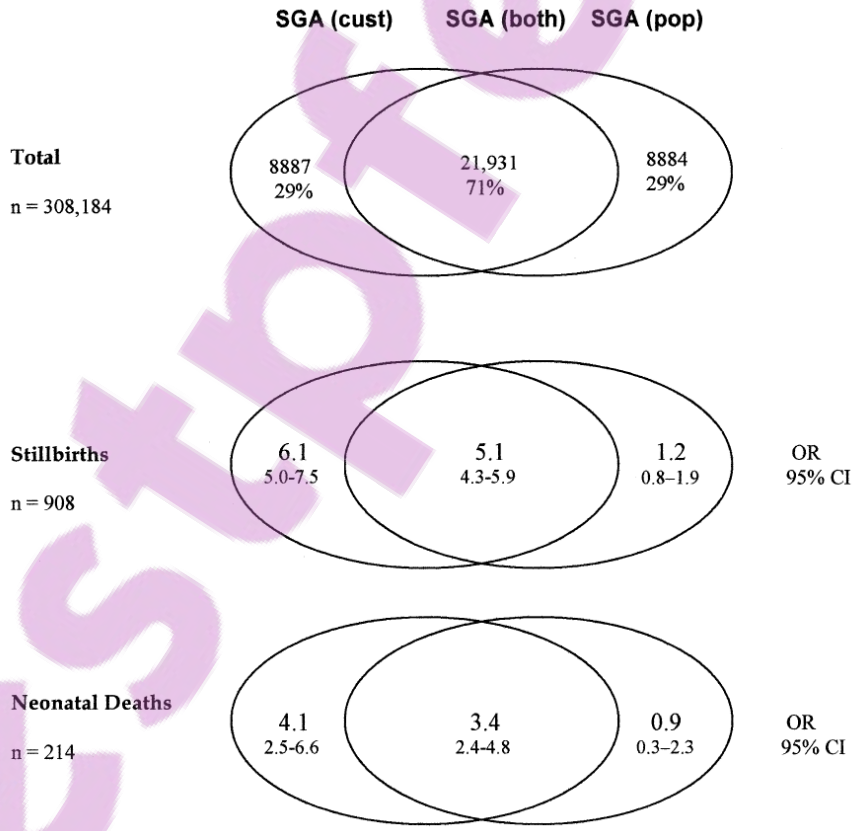


Figure 5.3. Association between SGA and adverse perinatal outcome in 308 184 Swedish births 1992-1995. The three categories are: (1) SGA by both methods, (2) SGA by customised percentile only and (3) SGA by population percentile only. Odds ratios and 95% Confidence Intervals are shown. Reprinted from Gardosi et al., Seminars in Perinatology (2004), Customized fetal growth standards: rationale and clinical application 28 (1) 33-40 with permission from Elsevier.

The birthweight customisation procedure as described by Gardosi and colleagues is currently the most widely studied customised birthweight model. Its use has been recommended by the Royal College of Obstetricians and Gynaecologists (Royal College of Obstetricians and Gynaecologists, 2002), and is currently in use at NWH (National Women's Health, 2012). The impact of maternal characteristics on individual birthweight is illustrated in Figure 5.4 where an infant with a birthweight of 3000g is considered normally grown for an Indian woman of small stature (chart A, 49th centile), while the same infant is considered growth restricted for a European woman of tall stature (Chart B, 5th centile)

Even though the observed differences at the individual level seem remarkable, the value of adding maternal characteristics to a birthweight model that uses an ultrasound-based fetal reference has been debated. Studies investigating perinatal mortality among SGA infants have suggested that the improved detection of at-risk infants is primarily due to the use of an

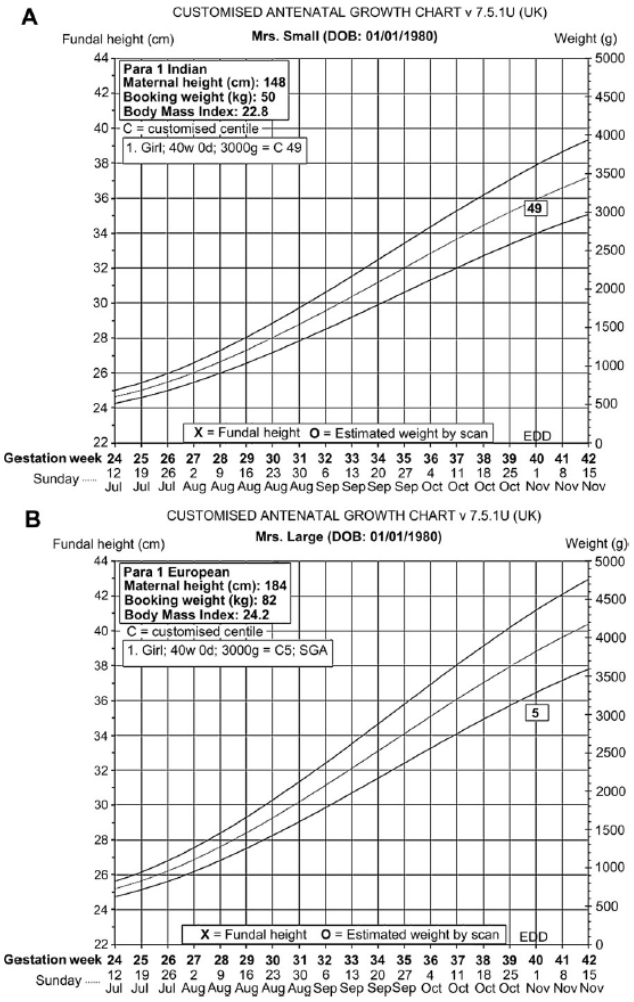


Figure 5.4. Customised antenatal growth charts for two mothers with different characteristics, with the resultant difference in growth curves illustrated by the respective centiles of the same birthweight plotted on each chart. Reprinted from Clinics in Perinatology 38 (1) Gardosi et al. Clinical strategies for improving the detection of fetal growth restriction , 21-31, 2011, with permission from Elsevier.

ultrasound fetal weight reference at preterm gestations (Larkin, Hill, Speer, & Simhan, 2012; X. Zhang, R. W. Platt, et al., 2007), and the inclusion of maternal characteristics doesn't further improve detection of at-risk infants (Hutcheon et al., 2008; Hutcheon, Zhang, & Platt, 2009; Hutcheon, Zhang, Platt, Cnattingius, & Kramer, 2011). These authors argue both that the increased risk of perinatal death among SGAcust infants is 'artifactual' as customisation identifies more preterm births as SGA (Hutcheon et al., 2011; Larkin et al., 2012; X. Zhang, R. W. Platt, et al., 2007), and that although maternal characteristics have statistically significant associations with birthweight, there are 'too many other unexplained influences on birth weight for meaningfully accurate prediction of birthweight at the individual level' (Hutcheon, Walker, & Platt, 2010). Despite this, a study by Zhang and colleagues (from the above group) in a subgroup analysis that was underpowered, found a non-significant increase in risk of adverse perinatal outcome among infants identified as SGA only by a customised birthweight model (RR 2.09, 95% CI 0.96–4.54), while there was no increase in adverse perinatal outcome in infants identified as SGA only by an ultrasound birthweight model (RR 1.04, 95% CI 0.42–2.55) (J. Zhang, Mikolajczyk, Grewal, Neta, & Klebanoff, 2011). In addition, Hutcheon and colleagues investigated customised birthweight versus ultrasound fetal weight and found no difference in detection of SGA infants at-risk of perinatal death between models. However they used an historical Swedish cohort that was predominantly European and non-obese, and the customised birthweight model was not directly comparable to the Gardosi model as there was no adjustment or exclusion for pathology and variables were included such as BMI categories instead of continuous height and weight (Hutcheon et al., 2008). A direct comparison of customised birthweight versus an ultrasound birthweight model is presented in Chapter 6.

Other customisation procedures have been described whereby further predictive variables are included in the modelling of birthweight (Pain et al., 2006), however even with ten additional variables Bukowski and colleagues only increased their model's ability to explain birthweight variability by 7% (Gardosi model R^2=27% (Gardosi & Francis, 2009b), Bukowski model R^2=35% (Bukowski et al., 2008)). This small increase in explanatory power comes at the expense of a substantially more complex algorithm that also requires variables such as years of education, altitude of residence and several early pregnancy biomarkers, limiting its usefulness. The small R^2 of this more complex model also illustrates how the majority of determinants of birthweight remain unknown.

The majority of research using customised birthweight centiles is retrospective and observational, where infants are weighed after birth and a centile calculated. However Gardosi and colleagues, following the principle of birthweight customisation, also created personalised antenatal growth charts where the limits of symphysis-fundal height are plotted prospectively (10^{th} and 90^{th} centiles customised according to the characteristics of the woman, (Mongelli &

Gardosi, 1999), Figure 5.4 and Figure 5.5). Estimated fetal weight from ultrasound scanning is also plotted on these same charts, and any measurement below the 10th customised or crossing centiles is considered pathological whereby increased antenatal surveillance is recommended (Gardosi, 2011). The antenatal use of these growth charts is illustrated in Figure 5.5 where serial fundal height measurements (marked X) are made at antenatal visits. The points at which referral would be made for antenatal assessment (including ultrasound estimation of fetal weight) are A: the first fundal height assessment is below the 10th centile; B: consecutive measurements suggest static growth; C: consecutive measurements suggest slow growth; or D: consecutive measurements suggest accelerated growth, Figure 5.5.

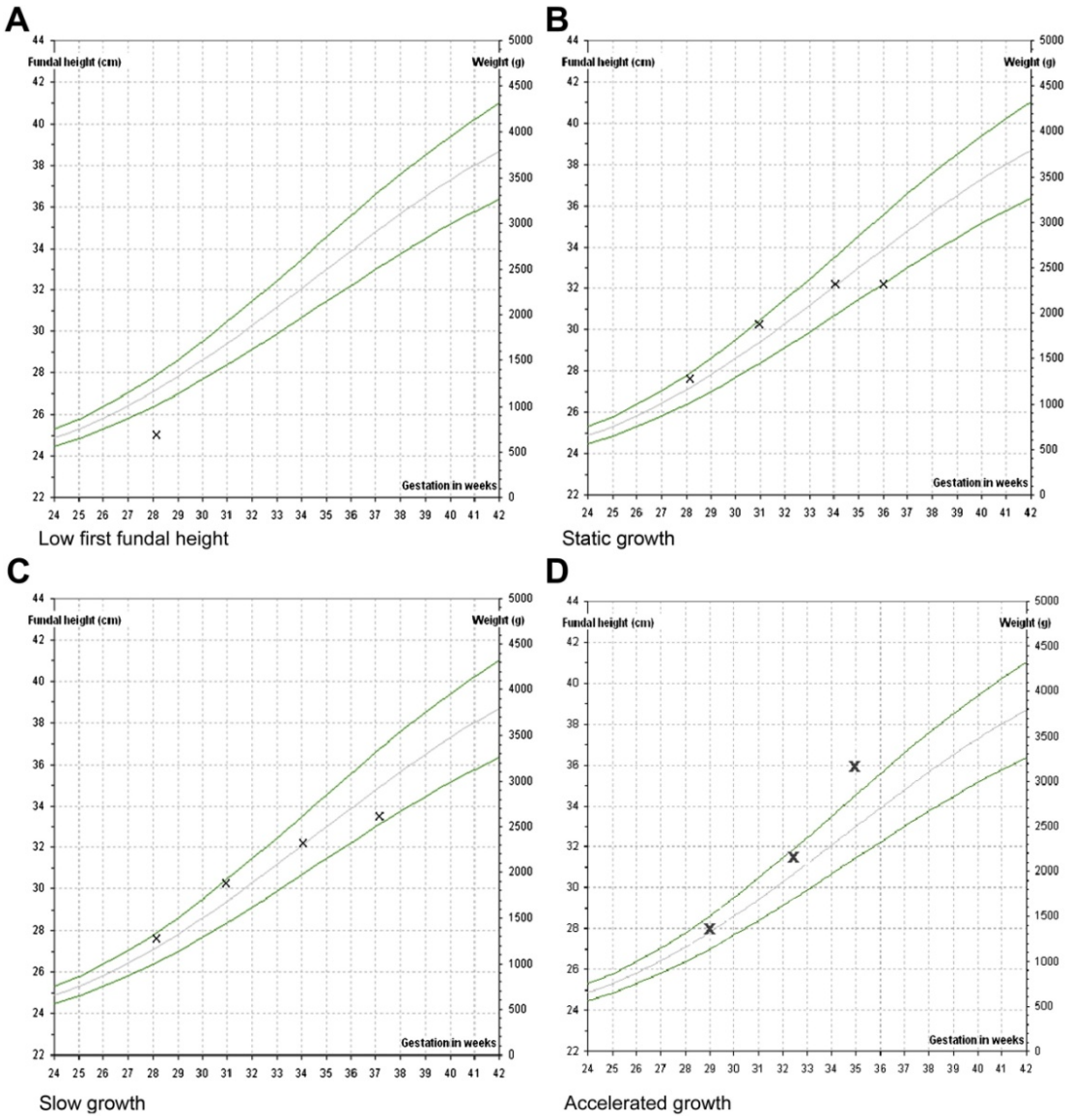


Figure 5.5. Examples of prospective use of customised antenatal growth charts and the points at which referral for further investigation would be instituted. Reprinted from Best Practice & Research Clinical Obstetrics and Gynaecology, 23 (6) Morse et al. Fetal growth screening by fundal height measurement, 809-18, 2009 with permission from Elsevier.

Limitations of antenatal charts include the reliance on ultrasound estimates of fetal weight which have an error of +/- 15%, with absolute error increasing with increasing gestational age (Australasian Society for Ultrasound in Medicine, 2001-2007a, 2001-2007b). However these same estimates are also used in population ultrasound references and always need to be interpreted with appropriate caution. Additionally, the ability to perform reliable symphysis-fundal measurements on obese mothers is limited, with SGA more likely to be missed in obese mothers compared with thin mothers (M. Williams et al., 2010). A Cochrane review of the antenatal use of customised growth charts compared with standard population growth charts concluded that in the absence of randomized controlled trials there was no evidence to suggest customised growth charts improved infant outcomes (Carberry et al., 2011). The use of customised antenatal charts has however lead to increased detection of SGA infants from 29% to 48% in the UK (Gardosi & Francis, 1999), and from 25% to 50% in an Australian setting (Roex et al., 2012). Given that antenatal detection of SGA can be associated with decreased adverse perinatal outcomes, improved identification of SGA is indirect evidence of a benefit (Lindqvist & Molin, 2005).

5.3.1. New Zealand customised birthweight centiles

NZ customised birth weight centiles were generated in 2004 using a birth cohort from 1993 to 2000 (L.M.E. McCowan, Stewart, Francis, & Gardosi, 2004). At that time maternal height, weight and smoking status were not routinely collected, which resulted in limited numbers of women with the complete data required to calculate a centile (n=4707, 8.0% of a total population of 59,064). Furthermore, as there was no information on smoking status, women who smoked remained in this analysis. As a result there were only six ethnic groups that had sufficient numbers for inclusion in the calculator; NZ European (n=1688, 36%) Māori (n=419, 9%), Samoan (n=506, 11%), Tongan (n=326, 7%), Chinese (n=751, 16%), Indian (n=214, 5%) and Other (n=803, 16%). Proportionally fewer Chinese women (7%) and more NZ European women (55%) were excluded with missing data. Additionally, as BMI was not routinely collected, those with complete data may have had a reason for BMI to be recorded, and this bias was evidenced by a disproportionately large number of women with diabetes in those with complete data. Bias was addressed in this study by randomly including a similar number of diabetic pregnancies to the rate in the total population, in ethnic-specific proportions.

Despite these limitations, the birthweight for the predefined standard European mother (3464g for a woman of height 163cm; weight 64kg; ethnic origin European; parity 0; infant sex neutral) was very similar to that obtained in Australia, America and Europe (Gardosi & Francis, 2009b), confirming not only the robustness of this method, but also the homogeneity among European populations around the world.

Since these centiles were created, more robust data collection at NWH means that we now not only have reliable data on height and weight, but also smoking, diabetes, hypertensive disease etc. that can also be included in analyses. The inclusion of women who smoked in the original dataset is likely to have particularly affected infant birthweights of Māori women, falsely lowering the optimum birthweight due to their high smoking rates in pregnancy (L. Dixon, Aimer, Guilliland, Hendry, & Fletcher, 2009). With the availability of more reliable data, it is timely to update the NZ centile coefficients with a modern cohort of women and inclusion of a greater number of New Zealand's ethnic groups, e.g. Cook Island Māori, Latin American, African etc. This analysis is presented in Chapter 6.

5.3.2. Method of Gardosi birthweight customisation

Detailed methods of the process of birthweight customisation are included in Appendix 2, however a brief overview follows:

The concept of customisation is to provide an optimal birthweight reference, against which an actual birthweight is compared. To do this, only birthweights of term infants (in accurately dated pregnancies) with no congenital anomalies or stillbirth are used in a multiple regression model. This model includes maternal and fetal physiological variables as well as pathological variables (which are subsequently excluded from the centile calculation, this is explained below). To facilitate comparisons between models from different populations, the regression model is centred on the characteristics of a standard mother (as mentioned above; maternal height 163cm; maternal weight 64kg; ethnic origin European; parity 0; infant sex neutral). A term optimal weight (TOW) for an individual infant can then be created using these regression coefficients, and as birthweight has a normal distribution, centiles can be created. The TOW is then adjusted for gestation using a 'proportionality growth function' derived from Hadlock's fetal weight equation (Hadlock et al., 1991). This fetal weight equation was created using ultrasound measurements from ongoing pregnancies with normal outcomes to healthy European women, but importantly it showed the variation in fetal weight with gestation (residuals of the model) was a constant percentage of mean fetal weight. As a result, the normal distribution of customised centiles can be adjusted for gestation by using the percentage variability of the term population. Once the infant is born, the actual birthweight is compared against the expected birthweight for that gestation and a birthweight centile is calculated.

The inclusion in the initial regression model of pathological variables such as diabetes, hypertensive disease and APH can at first be counter-intuitive to the concept of an optimal birthweight. It is important to note that none of the pathological variables are used in the calculation of the TOW. Instead, the effect of these variables on birthweight is accounted for by including them in the regression model, but the calculation of TOW assumes these pathologies are not present; in effect the coefficient for that variable is nought. Another method of excluding

these pathological influences on birthweight would be to exclude all women with these factors from the regression analysis. This is problematic in two ways; firstly it would result in smaller numbers and therefore less statistical power, and secondly there is a strong possibility that excluding women could lead to systematic bias, e.g. exclusion of smokers would bias the analysis to non-smokers, particularly influencing Māori women with high rates of smoking.

5.4. Screening for SGA

Early pregnancy prediction and screening for SGA is the subject of much research although to date no methods perform well enough for clinical use. Screening for SGA includes testing of biomarkers as well as ultrasound assessments of fetal size and uterine circulation through performing uterine artery Doppler studies. Early pregnancy biomarkers that have been shown to be associated with later SGA include low levels of β-hCG and pregnancy-associated plasma protein A (PAPP-A), high inhibin A or serum α-feto-protein (Figueras & Gardosi, 2011) as well as disturbances in angiogenic factors such as vascular endothelial growth factor (VEGF, placental growth factor (PlGF) and soluble vascular endothelial growth factor receptor-1 (sFlt-1) (see also Figure 3.11and section 3.4.2 above) (Poon, Syngelaki, Akolekar, Lai, & Nicolaides, 2012; J. Zhang et al., 2010). These biomarkers alone have low sensitivity and specificity for SGA. Additionally, abnormal uterine artery Doppler studies in early to mid gestation are also poor predictors of SGA (Chien, Arnott, Gordon, Owen, & Khan, 2000), although biomarker and Doppler studies both perform better in high risk pregnancies and for predicting early-onset disease (Figueras & Gardosi, 2011). A clinically useful screening test to predict SGA will likely involve a combination of clinical history, biomarkers and ultrasound assessments. A recently published algorithm of combined maternal characteristics, early pregnancy blood pressure, uterine artery Doppler studies and biomarkers (PAPP-A and PlGF) resulted in detection rates for pre-term SGA and term SGA of 55.5% and 44.3% for a false positive rate of 10.9% (Poon et al., 2012). Groups such as these, including the SCOPE (screening for pregnancy endpoints) consortium, will continue to work on improving screening tests to enable reliable prediction of SGA.

5.5. Summary

Fetal weight is determined by the interaction between genes and the environment. Multiple physiological and pathological factors influence fetal weight however the majority of determinants of normal birthweight currently remain unknown. Maternal characteristics have a substantial influence on birthweight and include maternal height, weight, ethnicity and parity. Other physiological contributors are infant gender and paternal genetic factors. In addition there are many known pathological influences on birthweight including cigarette smoking, hypertensive disease and maternal medical conditions. Dietary factors may also have a small role to play in facilitating fetal growth. Customised birthweight centiles attempt to account for

the physiological components of fetal growth, to better differentiate normal from abnormal fetal growth. Ultimately the development of robust early pregnancy screening tests for SGA (likely including clinical, ultrasound and biomarker components) will help identify those women at increased risk that would benefit from early pregnancy intervention (e.g. aspirin) and surveillance.

Chapter 6. | Maternal characteristics in customised birthweight centiles

6.1. Preamble

The manuscript reproduced below was published in the British Journal of Obstetrics and Gynaecology (BJOG) in April 2012. Prior to publication, we performed analyses comparing the previous NZ customised birthweight centile model to the new model as published below, and these analyses, which were not able to be included in the manuscript because of space limitations, follow this report (section 6.3 below).

Permission

Accepted 13 February 2012. Published Online 2 April 2012.

6.2. Manuscript: Maternal characteristics in customised birthweight centiles

Abstract

Objective: To regenerate coefficients for the New Zealand customised birthweight centile calculator using an updated birth cohort, and compare the identification of at-risk small-for-gestational-age (SGA) infants between full customisation (including maternal characteristics) and an ultrasound-based fetal weight and infant gender partial customisation.
Design: Retrospective cohort study of prospectively collected maternity data.
Setting: National Women's Health Auckland, New Zealand.
Population: Singleton pregnancies in the period 2006–2009; *n* = 24 176.
Methods: Multiple linear regression analysis was performed for full customisation (adjusted for gestation, infant gender, maternal characteristics and pathological variables) and ultrasound-and-gender customisation (adjusted for gestation and infant gender).
Main outcome measures: Risks of SGA-related perinatal death were compared between models.
Results: Changes occurred in some ethnicity coefficients, including Chinese (–135 g), Tongan (–101 g) and Samoan (–89 g), and ten ethnicities were added. Overall, full customisation identified SGA infants with higher odds of perinatal death (OR 5.6, 95% CI 3.6–8.7) than infants classed as SGA by ultrasound-and-gender customisation (OR 2.1, 95% CI 1.4–3.3) (*P* = 0.02). In subgroup

analyses, infants classed as SGA by full but not ultrasound-and-gender customisation (n = 888, 3.4%) had an increased risk of perinatal death (RR 4.7, 95% CI 2.7–7.9); however, those identified as SGA by ultrasound-and-gender customisation alone were not at an increased risk (n = 676, 2.6%, RR 1.1, 95% CI 0.4–3.6). The population attributable risk (PAR) of SGA-related perinatal death was higher for full (49.8%) than for ultrasound-and-gender (43.0%) customisation.

Conclusions: Updating the New Zealand customised birthweight centile calculator resulted in revised coefficients that better reflect a contemporary birth cohort. Inclusion of maternal characteristics in a birthweight customisation model increases the detection of SGA infants at risk of perinatal death.

Introduction

Small for gestational age (SGA) infants are at increased risk of perinatal morbidity and mortality (Gardosi & Francis, 2009a). Traditionally SGA has been defined as a birthweight of less than the tenth percentile using population-based standards and these population birthweight reference standards in Western countries are often derived from cohorts of predominantly European births which pre-date the obesity epidemic (Alexander, Himes, Kaufman, Mor, & Kogan, 1996; Thompson, Mitchell, & Borman, 1994). Due to the association between prematurity and fetal growth restriction (Morken, Kallen, & Jacobsson, 2006; Zeitlin, Ancel, Saurel-Cubizolles, & Papiernik, 2000), population birthweight reference standards under-diagnose SGA compared with intrauterine fetal growth standards (Gardosi, 2004; X. Zhang, Platt, Cnattingius, Joseph, & Kramer, 2007). Customised birthweight centiles, which use an intrauterine fetal weight reference and also adjust for maternal and fetal physiological factors, better identify SGA infants at risk of perinatal morbidity and mortality compared with infants classified SGA by population centiles alone (Gardosi & Francis, 2009a; L. M. E. McCowan, Harding, & Stewart, 2005).

Some authors have suggested that the improved association between customised SGA and adverse perinatal outcomes predominantly stems from the use of an intrauterine fetal weight reference at preterm gestations (Hemming, Hutton, & Bonellie, 2009; Larkin, Hill, Speer, & Simhan, 2012; X. Zhang et al., 2007), and that after adjustment for infant gender, further customisation using maternal characteristics such as height, weight and parity confers little added benefit (Hutcheon, Zhang, Cnattingius, Kramer, & Platt, 2008; Hutcheon, Zhang, Platt, Cnattingius, & Kramer, 2011). These previous studies have been performed in non-obese, predominantly European cohorts and may therefore have underestimated the effect of maternal characteristics on birthweight.

We have previously published New Zealand coefficients for customised birthweight centiles derived from a birth cohort at National Women's Health (NWH), Auckland, in the period 1993–

2000 (L.M.E. McCowan, Stewart, Francis, & Gardosi, 2004); however, the subgroup of women used to generate these coefficients may not have been representative of the total birthing population. Current data collection in our hospital now includes all of the variables required for generating fully customised birthweight centile models. We are now able to update our calculator using a large contemporary birth cohort and to account for pathological factors associated with birthweight such as smoking, hypertensive disease and diabetes (Gardosi & Francis, 2009b; Groom, North, Poppe, Sadler, & McCowan, 2007; L.M.E. McCowan et al., 2009). With this large multi-ethnic cohort with high rates of overweight and obese women, we are also able to investigate whether additional benefit is gained by excluding the effects of pathological factors and adjusting for maternal physiological characteristics in a full customisation model, compared with a partial customisation model that uses the same ultrasound fetal weight reference adjusted for infant gender alone.

The primary aims of the current study were therefore to: (1) regenerate coefficients for the New Zealand customised birthweight centile calculator using a large, updated birth cohort, and (2) compare full customisation with customisation adjusted for an ultrasound fetal weight reference and infant gender alone. We hypothesised that full customisation would better identify SGA infants at risk of perinatal mortality than an ultrasound-and-gender customisation model.

Methods

The NWH clinical database of births from 2006 to 2009 was used for the present cohort study. NWH is a tertiary referral hospital in Auckland, New Zealand, with a diverse ethnic population and approximately 7500 maternities per year. The NWH database of births consists of de-identified, prospectively collected maternity data for all births occurring at greater than or equal to 20 weeks of gestation, and includes demographic data, antenatal complications, and detailed delivery and newborn data. Data are routinely checked for completeness, out-of-range values and inconsistency (National Women's Health, 2010). Ethical approval for this study was gained from the Northern X Regional Ethics Committee (NTX/09/179/EXP).

Included in the study were women booked to deliver at NWH from January 2006 to December 2009 with singleton pregnancies n = 29 573. Consistent with previous methodology (Gardosi, Mongelli, Wilcox, & Chang, 1995; L.M.E. McCowan et al., 2004), the population used to calculate birthweight customisation coefficients excluded pregnancies with major congenital abnormalities, preterm birth (<37 weeks of gestation) and stillbirth, Figure 6.1. The eligible study population consisted of 26 611 women. Of these, 2429 (9.1%) had incomplete or missing data on one or more variable required to generate centile coefficients: 2033 (7.6%) were missing height, 1599 (6.0%) were missing weight and 352 (1.3%) were missing smoking status. An additional six women could not be classified into one of our ethnicity categories (recorded

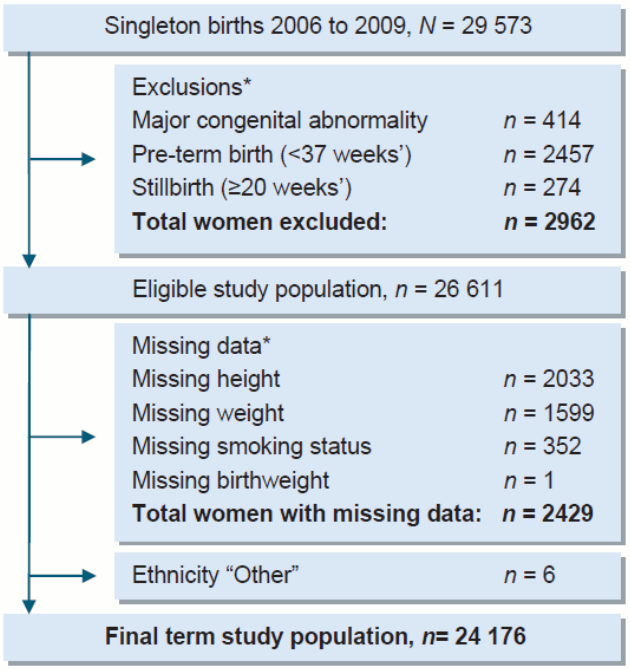


Figure 6.1. Flow of study participants.
***More than one exclusion criteria or missing data variable may apply to the same pregnancy, so numbers do not total.**

ethnicity as 'Other'), and so were excluded, leaving a final term study population of 24 176 women, Figure 6.1.

The physiological and pathological variables included in the full customisation multivariable analysis are variables that have previously been found to be associated with birthweight, and are included in previously published full customisation models (Gardosi & Francis, 2009b; Gardosi et al., 1995): i.e. maternal height, weight, parity, ethnicity, gestation, infant gender, cigarette smoking, diabetes, hypertensive disease and antepartum haemorrhage (APH). Maternal height and weight were recorded at the first antenatal booking visit and measured to the nearest centimetre and kilogram, respectively[3]. Parity was defined as the number of times a woman had given birth to liveborn infant(s) of any birthweight or gestation, or to a stillborn infant after 20 weeks of gestation or where the infant weighed 400g or more if gestation was unknown (Bai, Wong, Bauman, & Mohsin, 2002). Self-determined ethnicity was grouped and prioritised according to New Zealand Ministry of Health guidelines (Ministry of Health, 2004). The ethnicities included were NZ European, Māori, Fijian, Niuean, Tongan, Cook Island Māori, Samoan, Other Pacific Peoples, South East Asian, Indian (including Fijian Indian), Chinese, Other Asian, Latin American/Hispanic, African, Middle Eastern, and Other European. South East Asian ethnicity includes women from countries such as Vietnam, Thailand and Indonesia, and Other

[3] Gestation at booking was not able to be included as this was not recorded.

Asian includes women from the Indian subcontinent (excluding India), as well as Japan, Korea and others.

Gestational age was derived from the first day of the last menstrual period (LMP) if known, or by ultrasound if the LMP was unknown. Pregnancies were routinely dated during second trimester fetal anomaly scanning between 18 and 20 weeks of gestation. The estimated date of delivery (EDD) was only adjusted if fetal ultrasound measurements differed from the LMP gestation by more than 7 days before 20 weeks of gestation, or by >2 SD after 20 weeks of gestation, according to the Australasian Society for Ultrasound in Medicine guidelines (Australasian Society for Ultrasound in Medicine, 2001-2007a, 2001-2007b).

Cigarette smoking status was recorded both at booking and at delivery. If a woman was smoking at either time point she was defined as a smoker for the purposes of this study. Diabetes included either a pre-existing diagnosis of diabetes (type–1 or type–2 diabetes mellitus) or gestational diabetes mellitus (GDM). GDM was diagnosed by a 75–g oral glucose tolerance test with a fasting venous plasma glucose level of ≥ 5.5 mmol/l, and/or at 2 hours of ≥ 9.0 mmol/l adhering to the Australasian Diabetes in Pregnancy Society guidelines (Hoffman, Nolan, Wilson, Oats, & Simmons, 1998). Hypertensive disease included all women with chronic hypertension, gestational hypertension or pre-eclampsia as defined by the International Society for the Study of Hypertension in Pregnancy (Brown, Lindheimer, de Swiet, Van Assche, & Moutquin, 2001). For the purposes of this study, APH was defined as vaginal bleeding from any cause at or beyond 20 weeks of gestation after excluding placenta praevia (National Women's Health, 2010). Placenta praevia was excluded from this definition as it has not been associated with clinically important reductions in birthweight (Ananth, Demissie, Smulian, & Vintzileos, 2001).

For the second aim, comparing perinatal mortality between full and ultrasound-and-gender customisation, in addition to the term population, the total study population included women with preterm birth and stillbirth, resulting in a sample of 25 976 women[4]. Perinatal death included both stillbirths (defined as birth of an infant with no signs of life at 20 weeks of gestation or later, or where the infant weighed 400g or more, if gestation was unknown) and neonatal deaths (defined as death within the first 28 days of life of a liveborn infant born at 20 weeks of gestation or later, or with a birthweight of ≥400g, if gestation was unknown) (National Women's Health, 2010).

Statistical Methods

The method of full customisation used is as described by Gardosi et al (Gardosi, 2004; Gardosi et al., 1995). Coefficients for predicting birthweight were created in the term study population using multiple linear regression analysis (Gardosi et al., 1995; L.M.E. McCowan et al., 2004). The

[4] Of the final n=25 976 women, n=11 were unbooked and n=32 were transfers from other hospitals

full customisation model included gestational age, infant gender, maternal characteristics (ethnicity, height, weight, and parity) and pathological factors (smoking, diabetes, hypertensive disease and APH). Coefficients to the third order (linear, quadratic and cubic) are required for gestation and booking weight as the relationship between these variables and birthweight is not linear. To allow comparison with previous studies, coefficients are presented representing a 'standard mother' (Gardosi & Francis, 2009b): i.e. a nulliparous European woman of height 163cm and booking weight 64kg delivering at a gestational age of 280 days with the infant's gender unspecified. The ultrasound-and-gender customisation model included gestational age and infant gender alone and is equivalent to models previously used by Gardosi et al (Gardosi, Clausson, & Francis, 2009) and Hutcheon et al. (Hutcheon et al., 2008). The R^2 statistic was compared between each multivariable model (full and ultrasound-and-gender) using the *F*-test.

Birthweight centiles for both full and ultrasound-and-gender models were calculated for the total study population (*n*=25 976). To create birthweight centiles, an individual term optimal birthweight (TOW) is calculated using all the coefficients from the regression model except (in the case of full customisation) smoking, diabetes, hypertensive disease and APH. This is the equivalent of using the previously generated regression model and assuming that all the TOWs are derived from a population of non-smokers with no diabetes, hypertensive disease or APH, i.e. excluding pathological factors. Adjustment for gestation is then provided by applying a proportionality growth function derived from Hadlock's ultrasound-based fetal weight equation (Gardosi et al., 1995; Hadlock, Harrist, & Martinez-Poyer, 1991), and this gives a gestation related optimal weight (GROW). The actual birthweight is then compared with the GROW normal range, and a centile is generated (Gardosi et al., 1995).

SGA was defined as a birthweight less than the tenth centile using either the full customisation model (SGAfull) or the partial model of ultrasound-and-gender customisation (SGAus). Separate odds ratios (ORs) of perinatal death for SGAus infants and SGAfull infants were calculated through logistic regression analysis and compared using the Wald test.

Infants were grouped into four categories relative to their SGA status: non-SGA by both criteria; SGA by ultrasound-and-gender customisation alone; SGA by full customisation alone; and SGA by both criteria. The relative risk (RR, 95% CI) of perinatal death (stillbirth and neonatal death) for each group was calculated using non-SGA by both criteria as the reference group. Perinatal mortality was also compared between models by calculating the population-attributable risk (PAR) of SGA-related perinatal death (Rockhill, Newman, & Weinberg, 1998). PARs were calculated for full customisation and ultrasound-and-gender customisation using commonly used definitions of SGA (below the third, fifth and tenth customised centiles).

All statistical tests were performed using SAS 9.2 (SAS Institute Inc., Cary, NC, USA).

Table 6.1. Characteristics of term study population by maternal ethnicity

Ethnicity	*n* (%)	Smoker	Nulliparous	Maternal age (years)	Weight (kg)*	Height (cm)	Birthweight (g)
NZ European	9792 (40.5)	630 (6.4)	4875 (49.8)	33.0 (4.9)	65 (59–74)	166.6 (6.4)	3541 (458)
Other European	2303 (9.5)	102 (4.4)	1309 (56.8)	32.9 (4.8)	64 (58–72)	166.3 (6.3)	3515 (477)
Māori	1720 (7.1)	620 (36.1)	707 (41.1)	27.7 (6.8)	76 (65–90)	166.0 (6.1)	3498 (486)
Samoan	1226 (5.1)	249 (20.3)	439 (35.8)	28.6 (6.4)	88 (75–105)	166.3 (6.1)	3662 (492)
Tongan	1108 (4.6)	173 (15.6)	324 (29.2)	28.8 (6.3)	93 (80–106)	167.3 (5.7)	3732 (499)
Chinese	2957 (12.2)	91 (3.1)	1752 (59.3)	30.9 (5.1)	56 (51–62)	161.5 (5.2)	3369 (433)
Indian	1678 (6.9)	31 (1.9)	875 (52.2)	29.9 (4.6)	61 (54–69)	159.1 (6.1)	3196 (422)
African	271 (1.1)	9 (3.3)	83 (30.6)	29.8 (5.9)	67 (60–77)	162.1 (6.9)	3452 (488)
Cook Island Māori	407 (1.7)	141 (34.6)	143 (35.1)	27.0 (6.8)	83 (71–100)	165.6 (6.0)	3566 (480)
Fijian	192 (0.8)	11 (5.7)	94 (49.0)	28.6 (5.7)	69 (60–84)	163.4 (7.0)	3448 (493)
Latin American	158 (0.7)	9 (5.7)	90 (57.0)	32.3 (4.6)	63 (56–70)	162.5 (6.5)	3493 (436)
Middle Eastern	392 (1.6)	12 (3.1)	171 (43.6)	29.2 (5.8)	64 (57–73)	161.4 (6.0)	3419 (464)
Niuean	323 (1.3)	80 (24.8)	117 (36.2)	27.0 (6.5)	85 (74–98)	164.4 (6.0)	3558 (495)
South-East Asian	379 (1.6)	10 (2.6)	198 (52.2)	31.3 (5.4)	56 (51–63)	158.3 (5.8)	3333 (491)
Other Asian	1160 (4.8)	45 (3.9)	642 (55.3)	31.2 (5.2)	56 (51–63)	159.2 (6.2)	3295 (455)
Other Pacific Peoples	110 (0.5)	21 (19.1)	46 (41.8)	29.3 (6.8)	82 (70–100)	164.4 (6.3)	3501 (525)
Total study population	**24 176 (100)**	**2234 (9.2)**	**11 865 (49.1)**	**31.3 (5.7)**	**65 (57–76)**	**164.7 (6.8)**	**3487 (479)**

Data are presented as n (%) and mean (SD), as appropriate.
***Presented as median (IQR).**

Results

In the term cohort used to derive the new customised centile coefficients (*n* = 24 176), substantial variation in maternal characteristics, birthweight and smoking rates was seen between ethnicities, Table 6.1. Mean gestational age at delivery was 39.3 weeks of gestation (SD 1.2 weeks) and there was little variation in gestation between ethnic groups. Diabetes was diagnosed in 6.2% (*n* = 1500) of pregnancies: GDM in 5.2% (*n* = 1250) type–2 diabetes in 0.6% (*n* = 162) and type–1 diabetes in 0.4% (*n* = 88). Hypertensive disease was present in 8.3% (*n* = 2011) of pregnancies; gestational hypertension 3.6% (*n* = 880), pre-eclampsia 2.4% (*n* = 591), and chronic hypertension 2.2% (*n* = 540).

Multiple regression coefficients for full customisation and ultrasound-and-gender customisation are presented in Table 6.2. The full customisation model explained significantly more of the variability in birthweight (R^2 = 31%) than the ultrasound-and-gender customisation model (R^2 = 18%) (P<0.001; Table 6.2). The R^2 values were unchanged after adjustment for the differing numbers of variables between models (adjusted R^2).

Ethnicity coefficients have changed from the previous New Zealand calculator (L.M.E. McCowan et al., 2004): for Chinese (-135g), Tongan (-101g) Samoan (-89g), and Indian (-61g) women. There was also a small change in the coefficient for Māori women (-5g). An additional ten ethnicity coefficients that were not available in the previous New Zealand calculator are presented in Table 6.2, along with coefficients for the pathological variables smoking, hypertensive disease and diabetes.

Within the total study population (*n* = 25 976), ultrasound-and-gender customisation identified 2859 (11.0%) SGAus infants, while full customisation identified 3071 (11.8%) SGAfull infants. Perinatal death occurred in 201 infants (seven per 1000 total births) with 86 deaths (43%) occurring in infants who were classified as non-SGA by both models (both non-SGA, 3.9 per 1000 total births, Table 6.3). Infants who were SGAus had twice the odds of perinatal death compared with non-SGAus infants, (OR 2.1, 95% CI 1.4–3.3), whereas SGAfull infants had a greater than five-fold increased odds of perinatal death compared with non-SGAfull infants, (OR 5.6, 95% CI 3.6–8.7). Overall, infants classed as SGA by full customisation had a greater odds of perinatal death than infants who were classed SGA by ultrasound-and-gender customisation (*P* = 0.02).

There were 888 (3.4%) infants who were SGAfull alone, and 676 (2.6%) infants who were SGAus alone, Table 6.3. Infants who were SGAus alone had a similar rate of perinatal death as both non-SGA infants (RR 1.1, 95% CI 0.4–3.6), whereas infants who were SGAfull alone had a greater than four-fold increased risk of stillbirth (RR 4.3, 95% CI 2.2–8.4), neonatal death (RR 5.4, 95% CI 2.2–12.9) and overall perinatal death (RR 4.7, 95% CI 2.7–7.9) compared to both non-SGA infants. Infants who were classified as SGA by both criteria had the greatest risk of perinatal death, (RR 11.4, 95% CI 8.5–15.2).

Table 6.2. Multiple linear regression coefficients (g) for full customisation and ultrasound-and-gender customisation models

	Study population *n* = 24 176					
	Full customisation			Ultrasound-and-gender customisation		
	Coefficient (g)	SE	*P*	Coefficient (g)	SE	*P*
Gestation (from 280 days)						
Linear term	21.5	0.56	<0.001	21.9	3.78	<0.001
Quadratic term	−0.28	0.036	<0.001	−0.25	0.039	<0.001
Cubic term	−0.0009	0.0029	0.79	−0.0007	0.0031	<0.001
Gender						
Female	−60.6	2.56	<0.001	−60.0	2.79	<0.001
Male	60.6	2.56	<0.001	60.0	2.79	<0.001
Maternal height (from 163 cm)						
Height	8.6	0.45	<0.001			
Booking weight (from 64 kg)						
Linear term	7.33	0.302	<0.001			
Quadratic term	−0.111	0.0125	<0.001			
Cubic term	0.0008	0.0001	<0.001			
Ethnic group						
European	Ref					
Māori	−71.8	11.0	<0.001			
Samoan	−4.6	13.0	0.73			
Tongan	23.4	13.9	0.09			
Chinese	−34.0	9.0	<0.001			
Indian	−210.5	11.0	<0.001			
African	−139.7	24.6	<0.001			
Cook Island Māori	−45.2	20.7	0.03			
Fijian	−90.6	29.0	0.002			
Latin American	4.0	31.9	0.90			
Middle Eastern	−90.9	20.6	<0.001			
Niuean	−76.3	23.0	<0.001			
South-East Asian	−34.8	21.2	0.10			
Other Asian	−88.1	12.9	<0.001			
Other European	−15.2	9.2	0.10			
Other Pacific Peoples	−55.9	38.3	0.14			
Parity						
Parity 1	120.1	5.8	<0.001			
Parity 2	164.9	8.7	<0.001			
Parity 3	140.9	14.3	<0.001			
Parity 4+	163.2	15.5	<0.001			
Pathological variables						
Hypertensive disease	−77.8	9.5	<0.001			
Diabetes	40.9	11.3	<0.001			
Smoker	−124.7	9.4	<0.001			
Antepartum haemorrhage	−61.3	13.5	<0.001			
Model						
Constant	3513			3553		
Standard error of model	396.6			433.7		
R^2 statistic*	0.31			0.18		

***F*-test of difference between R2 values; P < 0.001.**

Table 6.3. Perinatal death by SGA classification

	Both non-SGA *n* = 22 229		SGA_{us} only *n* = 676		SGA_{full} only *n* = 888		Both SGA *n* = 2183	
Perinatal death	86	(0.4%)	3	(0.4%)	16	(1.8%)	96	(4.4%)
	Ref.	–	1.1	(0.4–3.6)	4.7	(2.7–7.9)	11.4	(8.5–15.2)
Stillbirth	58	(0.3%)	3	(0.4%)	10	(1.1%)	79	(3.6%)
	Ref.	–	1.7	(0.5–5.4)	4.3	(2.2–8.4)	13.9	(9.9–19.4)
Neonatal death	28	(0.1%)	0	–	6	(0.7%)	17	(0.8%)
	Ref.	–	–	–	5.4	(2.2–12.9)	6.2	(3.4–11.3)

Data expressed as n, (%) and RR (95% CI).

The PAR of SGA-related perinatal death using full customisation was higher for all definitions of SGA (below the third, fifth and tenth centiles) when compared with ultrasound-and-gender customisation, Figure 6.2. Using the standard definition of SGA (below the tenth centile), 6.8% more perinatal deaths were attributable to SGAfull infants (PAR 49.8%) compared with SGAus infants (PAR 43.0%).

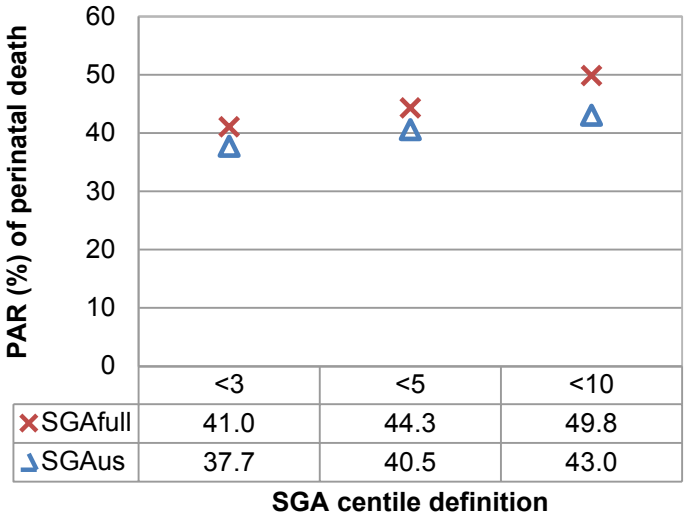


Figure 6.2. Population-attributable risk (PAR %) of SGA-related perinatal death by SGA centile definition for full customisation (SGAfull) and ultrasound-and-gender customisation (SGAus).

Discussion

We report updated coefficients and ten new ethnicity coefficients for a customised birthweight centile calculator in a large, multiethnic contemporary cohort of New Zealand women. We have demonstrated that the full customisation model identifies SGA infants that have significantly increased odds of perinatal death compared with SGA infants identified by a partial model, customised for ultrasound-and-gender alone. Full customisation identified an additional group of at-risk SGA infants (SGAfull only *n* = 888), who were not identified using ultrasound-and-gender customisation. These newly identified SGA infants have a greater than four-fold increased risk of perinatal death when compared to non-SGA infants. Full customisation also

resulted in a clinically important 6.8% increase in PAR of SGA-related perinatal death compared with ultrasound-and-gender customisation (SGAfull 49.8%, SGAus 43.0%). These findings support our hypothesis that excluding the effects of pathological factors and adjusting for maternal characteristics in a full customisation model better identifies SGA infants who are at-risk of perinatal mortality than an ultrasound-and-gender customisation model.

Infants who were identified as SGA by the previous New Zealand centile calculator have been shown to have an increased risk of perinatal morbidity and mortality (L. M. E. McCowan et al., 2005), but at the time those coefficients were generated much of the data required for the model were not routinely collected. Of 11 423 eligible participants in the previous study, 6459 (56.6%) were excluded due to missing height and/or weight data (L.M.E. McCowan et al., 2004). It is possible that non-random missing data could have contributed to bias in the previous study, such as women with specific pregnancy complications being more likely to have had height and weight measured. This potential bias in the previous study may explain the differences in some ethnicity coefficients reported in the current study. The correction of such bias by using updated and more complete data has resulted in a model that is likely to more accurately reflect the characteristics of our current obstetric population. Additionally, we are now able to account for the pathological effects of smoking, diabetes, hypertensive disease and APH in the calculation of optimal birthweight. Smoking, hypertensive disease and APH are associated with fetal growth restriction (Gardosi & Francis, 2009b; Groom et al., 2007; McCormack, Doherty, Magann, Hutchinson, & Newnham, 2008; L.M.E. McCowan et al., 2009) and diabetes is associated predominantly with increased fetal growth.(Ehrenberg, Mercer, & Catalano, 2004) By including pathological variables in the initial regression model but not including the coefficients for these pathological variables in the calculation of TOW, the resulting optimal birthweight reference range can be considered to be exclusive of pathology, i.e. a reference range for a non-smoker, non-diabetic with no hypertensive disease or APH. Another method to achieve this optimal birthweight reference range would be to exclude all women with these pathological features from the initial regression model; however, excluding such a large number of women would inevitably introduce non-systematic bias into the model. The above described adjustment to exclude pathological variables allows for the calculation of a more accurate true optimal birthweight.

Consistent with previous studies, the full customisation model explains significantly more variability in birthweight than the ultrasound-and-gender model (R^2 statistic 0.31 and 0.18 respectively, $P < 0.001$) (Gardosi et al., 2009; Hutcheon et al., 2008). The low R^2 value even for the full customisation model illustrates that the majority of variability in birthweight is not explained by variables included in this model. Other models that have attempted to predict birthweight with large numbers of variables, in addition to those used in full customisation, have

not resulted in substantial increases in predictive value, and the majority of determinants of birthweight are still unknown (Bukowski et al., 2008).

Sceptics of customised birthweight centiles have suggested that the addition of maternal characteristics does not add further benefit to a model which adjusts for an intrauterine fetal weight reference and infant gender (Hutcheon et al., 2008; Hutcheon et al., 2011; X. Zhang et al., 2007). Hutcheon et al. (Hutcheon et al., 2008) compared a modified full customisation model with the Hadlock ultrasound-based model and found no difference in risk of stillbirth or early neonatal death. Their Swedish cohort from 1992 to 2001 was predominantly European and non-obese, as was the low-risk white American cohort used to derive the Hadlock fetal growth standard (Hadlock et al., 1991). Additionally the risk of perinatal death was not investigated in infants who were SGA by a single criterion only. Similarly, in an analysis based on a low risk, predominantly white American cohort from greater than 20 years ago, Zhang et al. (J. Zhang, Mikolajczyk, Grewal, Neta, & Klebanoff, 2011) compared infants who were SGA (below the fifth centile) by the Hadlock ultrasound-based reference with those classed as SGA by full customisation, and found a similar risk of adverse perinatal outcomes in infants classed as SGA by either criteria (SGA by ultrasound, RR 2.68, 95% CI 2.00–3.58; SGA by full customisation RR 3.13, 2.34–4.18). Consistent with our findings, however, they also showed an increased risk of adverse perinatal outcome in those infants who were SGA by full customisation alone (RR 2.09, 95% CI 0.96–4.54), but not in the infants who were SGA by the ultrasound reference alone (RR 1.04, 95% CI 0.42–2.55).

Recently Mikolajczyk et al. (Mikolajczyk et al., 2011) published a method of birthweight customisation for global populations that presented stepwise analyses of adverse perinatal outcomes in SGA infants defined using increasing numbers of explanatory variables. In these non-European populations, customisation using the Hadlock ultrasound-based fetal weight reference alone consistently over-diagnosed SGA, with rates of SGA as high as 60%. Adjustment of the Hadlock model for country resulted in improved identification of SGA infants at-risk of adverse perinatal outcomes (RR 2.87, 95% CI 2.73–3.01) compared with Hadlock alone (RR 1.59, 95% CI 1.43–1.66), but the addition of maternal variables (height, weight and parity) to the adjusted model did not further improve the detection of at-risk SGA infants. As participating countries in this study have relatively homogenous populations, the adjustment for country can be considered a surrogate adjustment for ethnicity and the mean maternal characteristics (height, weight and parity) of that population. Subsequent adjustment for maternal characteristics in addition to country would not therefore be expected to substantially improve the performance of the model. As a result Mikolajczyk et al. have demonstrated that adjustment for maternal characteristics using the surrogate of country, improves the detection of adverse perinatal outcomes over Hadlock ultrasound customisation alone.

In our ethnically diverse population with a high proportion of overweight and obese women, there was considerable agreement in classification between full and ultrasound-and-gender customisation with 24 412 (94%) infants either non-SGA or SGA by both criteria. This degree of agreement is expected, as classification changes between models will only occur in infants that have a customised birthweight centile close to the tenth centile by either model. Customisation of birthweight by either model identified SGA infants who were at-risk of perinatal death; however, full customisation identified a higher risk population of SGA infants with a significantly increased odds of perinatal death compared with SGA infants defined by the ultrasound-and-gender model (SGAus OR 2.1, 95% CI 1.4–3.3; SGAfull OR 5.6, 3.6–8.7, $P = 0.02$).

The majority of perinatal deaths occurred in infants where classifications were concordant (both non-SGA and both SGA $n = 182$, 91%), and the highest risk of perinatal death occurred in the majority group of SGA infants who were SGA by both criteria ($n = 2183$, 44 per 1000 total births, RR 11.4, 95% CI 8.5–15.2). However, the infants who were newly identified as SGA by the full customisation model (SGAfull only $n = 888$, i.e. 24% of all SGA infants), were a high-risk group with a greater than four-fold increased risk of perinatal death compared with non-SGA infants. In contrast those infants who were SGAus alone ($n = 676$, 18%) did not have an increased risk of perinatal death compared with non-SGA infants. These findings suggest full customisation better identifies true growth restriction than ultrasound-and-gender customisation.

Further support for the advantages of full customisation was the higher PAR of SGA-related perinatal death when compared to the ultrasound-and-gender model. As PAR standardises risk comparisons by accounting for different numbers of 'exposed' pregnancies (infants identified as SGA by each model), direct comparisons between models can be made. Using a definition of SGA as infants born below the tenth centile, the full customisation model resulted in a PAR of SGA-related perinatal deaths that was 6.8% higher than was calculated by ultrasound-and-gender alone, which we believe is a clinically important increase.

As with previous analyses of customised birthweight standards, the applicability of our findings to clinical practice is limited to the identification of these at-risk SGA infants at birth when no intervention is possible other than postnatal monitoring.

The current study utilised prospectively collected hospital data, with robust data cleaning (National Women's Health, 2010). Overall 9% of the eligible study population had missing data. It is possible that the women with these missing data are non-random; however, with >90% complete data and large study numbers, this is unlikely to have a significant impact on our results. Additionally, some of the new ethnicity groups had small numbers, particularly Fijian ($n = 192$) and Latin American ($n = 158$) groups. As a result, these groups may not fully reflect the characteristics of their respective ethnicities; however, separate coefficients based on smaller

numbers will still estimate ethnicity characteristics better than combining women of diverse ethnicities into a heterogeneous 'Other' group.

Despite our large study population of 25 976, our sample is smaller than some other studies that have investigated maternal characteristics in birthweight customisation (Gardosi et al., 2009; Hutcheon et al., 2008). As perinatal death is a rare event, there were only 19 perinatal deaths in the subgroup analyses of SGA infants where classifications did not agree (SGAus only and SGAfull only). The major advantage of the current study population over previous cohorts is the heterogeneity of maternal characteristics, particularly ethnicity and maternal body mass index. It would be ideal if the subgroup analyses we have performed could be repeated in a larger multiethnic population to confirm our study findings.

Conclusions

New customised birthweight centile coefficients have been created using data from a large updated birth cohort with addition of new ethnicities to better reflect our current obstetric population.

We have shown that a full customisation model that excludes the effects of pathological factors, and adjusts for maternal characteristics, identifies SGA infants that are at higher risk of perinatal death than a partial customisation model that adjusts for ultrasound and gender alone. Additionally, the group of infants identified as SGA by full customisation alone have a greater than four-fold increased risk of perinatal death, whereas infants identified by ultrasound-and-gender customisation alone do not have an increased risk of perinatal death. Furthermore this full customisation model increases the PAR of SGA-related perinatal death by 6.8%. The inclusion of maternal characteristics and pathological variables in a birthweight customisation model is therefore of clinical utility.

6.3. Comparisons between the previous and new (2012) NZ customised birthweight models

In order to assess the impact of changing customised birthweight coefficients in our local NZ population, a comparison between the two (old and new) customised birthweight models in the identification of at-risk SGA infants was undertaken. This work was not published but is presented below.

Introduction

As part of the development of the new NZ customised birthweight model, we wished to compare the performance of the new model versus the previous (old) model in terms of identifying SGA infants at risk of adverse perinatal outcomes. We hypothesised that; (1) the new model would

better identify SGA infants who are at-risk of adverse perinatal outcome when compared to the old model, and (2) the risk of adverse neonatal outcomes would be increased in those infants newly diagnosed as SGA who had previously been classified as non-SGA.

Methods

This analysis used the same population and variable definitions as described in the Methods of section 6.2 above, and the inclusion and exclusion of participants is the same as illustrated in Figure 6.1. Multivariable linear regression to develop coefficients for the new model was performed as described in the Statistical Methods of section 6.2 above. After subsequent inclusion of infants with preterm births and stillbirths, two birthweight centiles were created for each infant (n = 25 976); one using the coefficients from the old model (L.M.E. McCowan et al., 2004), and one using coefficients from the new model. A comparison of the coefficients of the two models is presented in Table 6.5.

For each of the models, relative risks (RR, 95% CI) of adverse perinatal outcomes in SGA infants (perinatal death and preterm birth <37 weeks of gestation) were calculated using the referent group of non-SGA infants. RRs were then compared between calculators. To allow ethnicities categorised as 'Other' from the previous study to be compared, centiles for the new calculator were generated using the appropriate new ethnicity coefficients but this group remained classified as 'Other' ethnicity in subsequent analyses.

Similar to the previous analyses of SGAus and SGAfull, infants were grouped into four categories relative to their SGA status; non-SGA by both models (both non-SGA); SGA by the old model only (new non-SGA); SGA by the new model only (new SGA); and SGA by both models (both SGA). Demographics and outcomes were compared across all groups using the chi squared test for categorical data and analysis of variance (ANOVA) for continuous data. A P-value of <0.05 was considered significant. The RRs of preterm birth and perinatal death for each group were calculated using non-SGA by both models as the reference group.

All statistical tests were performed using SAS 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

The maternal demographic characteristics for the study populations included in the old and new calculators are presented in Table 6.4. The participants in the present study were also slightly older (mean 31.3y, SD 5.6 and 30.3y, 5.9 respectively), and more likely to be nulliparous (49.1% and 36.4% respectively) than those in the previous study.

Data were not available for pathological variables in the previous study, but the overall proportion of smokers in the present study population was 9.2% (n = 2234, Table 6.1 above) although this rate differed greatly by ethnicity, ranging from 1.9% among Indian women to

36.1% among Māori women. The prevalence of pathological pregnancy complications among this population were presented in the Results of section 6.2 above.

The new model gave an expected birthweight of 3513g for a standard mother, Table 6.5. A further 61g would be added if the infant was a male, and subtracted if the infant was a female. This is very similar to the values of 3464g and 58g respectively using coefficients from the old model, Table 6.5. Ethnicity coefficients have changed, with the greatest magnitude of change seen in the Chinese ethnicity coefficient (+101g with the previous calculator to -34g with the new calculator). Samoan and Tongan ethnicity coefficients were previously larger than the European referent, but the newly generated coefficients are not significantly different from European (*P*-values of 0.73 and 0.09 respectively). Table 6.5 also shows that ten further ethnicity coefficients have been added to the new model, and the pathological variables of smoking, hypertensive disease and diabetes have also been included where they previously were not available.

Overall, the old model identified 2517 (9.7%) of infants as SGA (SGAold), while the new model identified 3075 (11.8%) of infants as SGA (SGAnew), Table 6.6. SGA status was therefore changed between the old and new models in 648 (2.5%) of infants; non-SGAold to SGAnew (new SGA) in 603 (2.3%) infants and SGAold to non-SGAnew (new non-SGA) in 45 (0.2%) infants, Table 6.6. These re-classifications resulted from only small differences in absolute centiles. The majority of infants had concordant classifications between models (97.5% classified as both non-SGA or both SGA) with 80% of SGAnew infants also SGA by both models (*n* = 2472, Table 6.6). Consistent with this substantial overlap, infants classified as SGA by either calculator had an increased RR of both preterm birth and perinatal death, with the magnitude of the RR for each of these adverse perinatal outcomes similar between calculators, Figure 6.3.

The new SGA group included predominantly European infants (*n* = 468, 77.6%) which comprised 3.6% of all European births. A similar proportion of births to Māori women were re-classified as SGA using the new model (*n* = 70, 4.2%) but few women from other ethnicities were categorised as new SGA (Tongan *n* = 4, 0.3%; Samoan *n* = 2, 0.2%; Indian *n* = 31, 1.9%; Chinese *n* = 3, 0.1%; Other *n* = 25, 0.6%). There were very small numbers in the new non-SGA group, but 55.6% (*n* = 25) of these infants were Chinese, comprising 0.9% of all Chinese births. The additional ethnicities that made up the balance of the new non-SGA group were; Samoan (*n* = 10, 0.8%), Tongan (*n* = 4, 0.5%) and Other (*n* = 6, 0.3%).

Similar to the previous analyses between SGAfull and SGAus above, infants in the both SGA group had a significantly increased RR of adverse outcomes when compared to the both non-SGA group, including an eleven-fold increased RR of perinatal death, Table 6.6. Infants in the new SGA group had a three-fold increased RR of perinatal death, but no increase in risk of preterm birth, however the new SGA group had small numbers.

Table 6.4. Ethnic distribution and characteristics of new and previous study populations

Ethnicity	Included in study				Booking weight (kg)				Height (cm)				Birthweight (g)			
	old model		new model		old model		new model		old model		new model		old model		new model	
European	1688	35.9%	-	-	69.2	(14.6)	-	-	164.9	(6.7)			3520	(486)	-	-
NZ European	-	-	9792	40.5%	-	-	67.8	(13.2)	-	-	166.6	(6.4)	-	-	3541	(458)
Other European	-	-	2303	9.5%	-	-	66.4	(12.8)	-	-	166.3	(6.3)	-	-	3515	(477)
Māori	419	8.9%	1720	7.1%	78.4	(19.0)	79.4	(18.9)	164.7	(6.2)	166.0	(6.1)	3414	(509)	3498	(486)
Samoan	506	10.8%	1226	5.1%	86.6	(18.8)	91.3	(21.6)	164.2	(5.6)	166.3	(6.1)	3642	(504)	3662	(492)
Tongan	326	6.9%	1108	4.6%	88.4	(17.9)	94.6	(20.8)	167.3	(5.7)	167.3	(5.7)	3782	(519)	3732	(499)
Chinese	751	16.0%	2957	12.2%	55.9	(9.0)	56.9	(8.8)	159.3	(5.3)	161.5	(5.2)	3351	(428)	3369	(433)
Indian	214	4.5%	1678	6.9%	61.2	(13.3)	62.5	(12.1)	158.4	(6.0)	159.1	(6.1)	3132	(452)	3196	(422)
Other	803	17.0%	-	-	69.9	(19.6)	-	-	160.8	(6.6)	-	-	3446	(484)	-	-
African	-	-	271	1.1%	-	-	68.8	(13.3)	-	-	162.1	(6.9)	-	-	3452	(488)
Cook Island Māori	-	-	407	1.7%	-	-	86.4	(20.7)	-	-	165.6	(6.0)	-	-	3566	(480)
Fijian	-	-	192	0.8%	-	-	72.3	(17.5)	-	-	163.4	(7.0)	-	-	3448	(493)
Latin American	-	-	158	0.7%	-	-	64.5	(13.5)	-	-	162.5	(6.5)	-	-	3493	(436)
Middle Eastern	-	-	392	1.6%	-	-	66.0	(12.7)	-	-	161.4	(6.0)	-	-	3419	(464)
Niuean	-	-	323	1.3%	-	-	87.1	(17.8)	-	-	164.4	(6.0)	-	-	3558	(495)
Other Asian	-	-	1160	4.8%	-	-	58.3	(10.5)	-	-	159.2	(6.2)	-	-	3295	(455)
Other Pacific Peoples	-	-	110	0.5%	-	-	84.6	(19.8)	-	-	164.4	(6.3)	-	-	3501	(525)
Southeast Asian	-	-	379	1.6%	-	-	58.3	(11.0)	-	-	158.3	(5.8)	-	-	3333	(491)
Total	**4707**	**100%**	**24 176**	**100%**	**70.9**	**(18.7)**	**69.3**	**(17.5)**	**163.0**	**(6.7)**	**164.7**	**(6.8)**	**3474**	**(503)**	**3487**	**(479)**

Data are mean (SD) and *n* % of column or row totals as appropriate

Table 6.5. Comparison of multiple linear regression coefficients between old and new customised birthweight models.

	Old model *n* = 4707		New model *n* = 24 176		
	Coefficient	*P*	Coefficient	SE	*P*
Gestation (from 280 days)					
Linear term	19.5	<0.001	21.5	0.56	<0.001
Quadratic term	-0.28	0.003	-0.28	0.036	<0.001
Cubic term	0.0006	0.91	-0.0009	0.0029	0.79
Gender					
Female	-57.7	<0.001	60.6	2.56	<0.001
Male	57.7	<0.001	-60.6	2.56	<0.001
Maternal height (from 163cm)					
Height	9.6	<0.001	8.6	0.45	<0.001
Booking weight (from 64kg)					
Linear term	8.44	<0.001	7.33	0.302	<0.001
Quadratic term	-0.114	<0.001	-0.111	0.0125	<0.001
Cubic term	0.00065	0.017	0.0008	0.0001	<0.001
Ethnic group					
European†	ref	-	ref	-	-
Māori	-66.8	0.004	-71.8	11.0	<0.001
Samoan	84.2	<0.001	-4.6	13.0	0.73
Tongan	124.1	<0.001	23.4	13.9	0.09
Chinese	100.9	<0.001	-34.0	9.0	<0.001
Indian	-149.5	<0.001	-210.5	11.0	<0.001
Other	13.3	0.48	-	-	-
African	-	-	-139.7	24.6	<0.001
Cook Island Māori	-	-	-45.2	20.7	0.03
Fijian	-	-	-90.6	29.0	0.002
Latin American	-	-	4.0	31.9	0.90
Middle Eastern	-	-	-90.9	20.6	<0.001
Niuean	-	-	-76.3	23.0	<0.001
South-East Asian	-	-	-34.8	21.2	0.10
Other Asian	-	-	-88.1	12.9	<0.001
Other European	-	-	-15.2	9.2	0.10
Other Pacific Peoples	-	-	-55.9	38.3	0.14
Parity					
Parity 1	102	<0.001	120.1	5.8	<0.001
Parity 2	102	<0.001	164.9	8.7	<0.001
Parity 3	123	<0.001	140.9	14.3	<0.001
Parity 4+	176	<0.001	163.2	15.5	<0.001
Pathological variables					
Hypertensive disease	-	-	-77.8	9.5	<0.001
Diabetes	-	-	40.9	11.3	<0.001
Smoker	-	-	-124.7	9.4	<0.001
Antepartum haemorrhage			-61.3	13.5	<0.001
Model					
Constant	3464	-	3513	-	-
Standard error of model	420.4	-	396.6	-	-

SE, standard error

† Old model referent group is all European, new model referent group is New Zealand European

Table 6.6. Demographic characteristics and outcomes by SGA classification

	New model non-SGA				New model SGA				
	Both non-SGA*		New non-SGA†		New SGA‡		Both SGA§		P**
	n = 22 856		*n* = 45		*n* = 603		*n* = 2472		
Demographic characteristics									
Maternal age	31.3	(5.7)	29.0	(6.3)	32.4	(5.4)	31.0	(6.0)	<0.01
Maternal height	164.6	(6.8)	164.1	(6.5)	165.0	(6.5)	164.5	(6.8)	0.43
Maternal weight	69.1	(17.4)	75.3	(22.0)	67.8	(13.6)	72.5	(19.8)	<0.01
European ethnicity¶	11 484	50.3%	0	0.0%	468	77.6%	1,002	40.5%	<0.01
Smoker	1971	8.6%	4	8.9%	94	15.6%	406	16.4%	<0.01
Nulliparous	11 162	48.8%	28	62.2%	275	45.6%	1282	51.9%	<0.01
Outcomes									
Birth weight	3509	(513)	2982	(268)	2,939	(365)	2,563	(619)	<0.01
Centile (new coefficients)	50.9	(29.4-74.6)	10.5	(10.2-10.8)	8.6	(7.8-9.4)	3.8	(1.6-5.8)	<0.01
Gestation (w)	39.0	(1.9)	39.1	(1.5)	39.0	(2.2)	37.9	(3.6)	<0.01
Preterm birth (<37 weeks)	1286	5.6%	2	4.4%	35	5.8%	425	17.2%	<0.01
RR [95%CI]	ref	-	0.79	[0.20- 3.07]	1.15	[0.79- 1.71]	3.06	[2.76- 3.38]	
Perinatal death	89	0.4%	0	0.0%	7	1.2%	105	4.3%	<0.01
RR [95%CI]	ref	-	-	-	2.98	[1.39- 6.41]	10.91	[8.25- 14.42]	

Data expressed as *n* %, mean (SD), median (inter-quartile range) or Relative Risk [95% confidence interval] as appropriate.

*** non-SGA by both old and new models**

† new model changes classification from SGA to non-SGA

‡ new model changes classification from non-SGA to SGA

§ SGA by both old and new models

**** *P*-value of ANOVA or chi-squared test for differences across all groups**

¶ NZ European and Other European combined

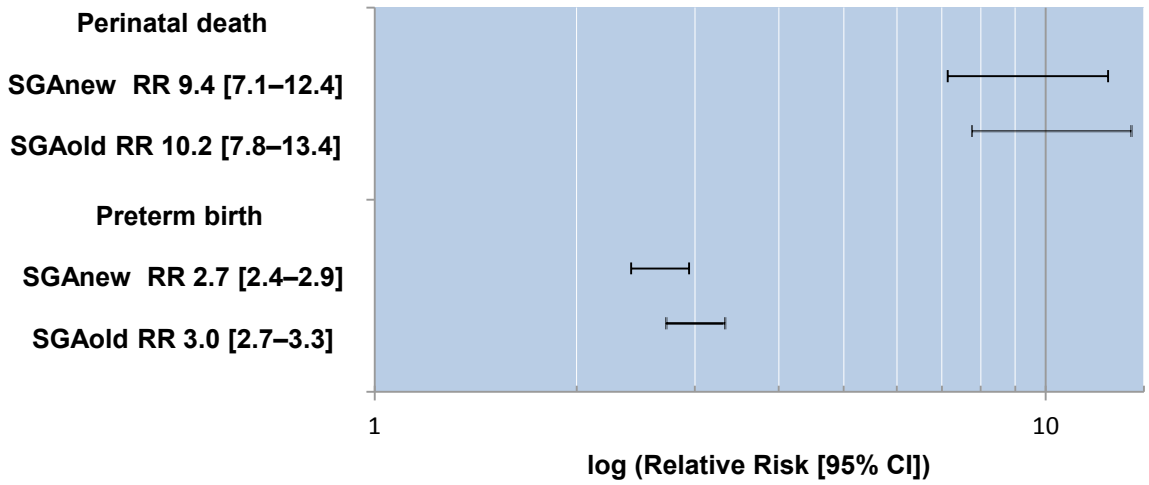


Figure 6.3. Relative Risk, RR [95% CI] of perinatal death and preterm birth by SGA status using old and new calculators.

Discussion

The new updated coefficients for the NZ customised birthweight model identified 603 (2.3%) additional infants as SGA and reclassified 45 (0.2%) as non-SGA compared with the previous model. As this new SGA group had a three-fold increase in risk of perinatal death, the updated calculator appears to have identified a small additional group of at-risk SGA infants. The cost of identifying these at-risk infants is an increase in the overall number of infants classified as SGA therefore, contrary to our hypothesis, the overall performance of the two calculators in terms of SGA-associated preterm birth and perinatal mortality is similar.

Despite the data limitations of the previous model (see Discussion of section 6.2 above), infants who are SGA using the old model coefficients have been shown to have an increased risk of perinatal morbidity and mortality (L. M. E. McCowan et al., 2005). The new model uses data that has more robust collection and cleaning, meaning the observed changes in ethnicity coefficients are more likely to reflect the characteristics of our current obstetric population. Although true changes in demographic characteristics may have occurred between the two study periods (Table 6.4) with the present study population also being older and more likely to be nulliparous, these differences may also represent differences in data quality between the two studies.

The constant of our model of 3513g (the optimal term birthweight of the standard mother), is similar to multiple previous international studies (Gardosi & Francis, 2009b, 2012), suggesting that women of European origin have similar physiological birthweight influences regardless of where they live. This finding is also consistent with the lack of difference in coefficients between NZ European and Other European in our own model, Table 6.. In the new model, the ethnicity coefficients for Samoan and Tongan women are no longer significantly different from European,

suggesting that these ethnicities do not have an influence on birthweight that is different from European. Well described differences in mean birthweights between these ethnic groups must therefore result from other factors such as maternal weight, height, parity and/or differences in pathological influences on birthweight. The newly generated coefficients for Latin American, SouthEast Asian and Other Pacific Peoples also have non-significant differences compared to New Zealand European, possibly due to small numbers meaning these groups may not fully reflect the characteristics of their respective ethnicities, or it may be that these groups are truly no different from European. As previously mentioned, despite small numbers of women in some ethnic groups, separate ethnicity coefficients are still likely to better estimate the characteristics of these groups than classifying women into a mixed "Other" group.

When compared to the previous model coefficients, all ethnicity coefficients in the new model were smaller or more negative relative to the European referent group, with the greatest magnitude of change in Chinese women (135g) and the smallest change in Māori women (6g). This finding could be explained by bias towards under-estimation of optimal birthweight in the referent European ethnic group in the original study, possibly due to the large number of women excluded from this former analysis due to non-random missing data. Correction of a previous under-estimation of birthweight in European women would result in a relative negative change in coefficients for all other ethnicities, i.e. coefficients becoming smaller or more negative. Under-estimation of optimal birthweight in European women in the old model would lead to a small under-diagnosis of SGA, consistent with our finding that 78.0% of new SGA infants were of European ethnicity. Ethnicity coefficients will also be influenced by the addition of pathological variables to the model, e.g. varying rates of pathology between ethnicities. In particular, smoking status was not available at the time of the previous study and this may explain some of the changes in ethnicity coefficients. The proportion of pregnant women who smoke in NZ differs greatly between ethnicities as illustrated in Table 6.1. The inclusion of smokers in the previous study population would have had an influence on optimal birthweight for each ethnicity which was influenced by their rates of smoking in pregnancy. However despite the observed changes in coefficients between calculators, absolute centile changes were small, with mean centile change varying by ethnicity ranging from –3.9 centile (SD 2.4) in European to +4.6 centile (SD 2.8) in Chinese (data not shown). As a result only small overall numbers of infants were reclassified as SGA or non-SGA.

Conclusion

The new customised birthweight model has been created using data from a large modern birth cohort with addition of new ethnicities to better reflect our current obstetric population. The updated model identified more infants at-risk of perinatal death however this was at the

expense of increasing the overall number of pregnancies classified as SGA. As a result the performance of the new calculator at identifying at-risk infants is equivalent to the performance of the previous calculator. Despite the similar overall performance, updating the birthweight centile calculator with modern data is a valuable exercise as more ethnicities are now represented and there is less bias created by missing data.

References

Alexander, G. R., Himes, J. H., Kaufman, R. B., Mor, J., & Kogan, M. (1996). A United States national reference for fetal growth. *Obstetrics & Gynecology, 87*(2), 163-168.

Ananth, C. V., Demissie, K., Smulian, J. C., & Vintzileos, A. M. (2001). Relationship among placenta previa, fetal growth restriction, and preterm delivery: a population-based study. *Obstetrics & Gynecology, 98*(2), 299-306.

Australasian Society for Ultrasound in Medicine. (2001-2007a). Guidelines for the mid trimester obstetric scan *Policies and Statements D2*. http://www.asum.com.au/site/policies.php: ASUM.

Australasian Society for Ultrasound in Medicine. (2001-2007b). Statement on normal ultrasonic fetal measurements *Policies and Statements D7*. http://www.asum.com.au/site/policies.php: ASUM.

Bai, J., Wong, F. W., Bauman, A., & Mohsin, M. (2002). Parity and pregnancy outcomes. *American Journal of Obstetrics & Gynecology, 186*(2), 274-278.

Brown, M. A., Lindheimer, M. D., de Swiet, M., Van Assche, A., & Moutquin, J. M. (2001). The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). *Hypertension in Pregnancy, 20*(1), IX-XIV.

Bukowski, R., Uchida, T., Smith, G. C., Malone, F. D., Ball, R. H., Nyberg, D. A., . . . for the First and Second Trimester Evaluation of Risk (FASTER) Research Consortium. (2008). Individualized Norms of Optimal Fetal Growth: Fetal Growth Potential. *Obstetrics & Gynecology, 111*(5), 1065-1076.

Ehrenberg, H. M., Mercer, B. M., & Catalano, P. M. (2004). The influence of obesity and diabetes on the prevalence of macrosomia. *American Journal of Obstetrics & Gynecology, 191*(3), 964-968.

Gardosi, J. (2004). Customized fetal growth standards: rationale and clinical application. *Seminars in Perinatology, 28*(1), 33-40.

Gardosi, J., Clausson, B., & Francis, A. (2009). The value of customised centiles in assessing perinatal mortality risk associated with parity and maternal size. *BJOG: An International Journal of Obstetrics & Gynaecology, 116*(10), 1356-1363.

Gardosi, J., & Francis, A. (2009a). Adverse pregnancy outcome and association with small for gestational age birthweight by customized and population-based percentiles. *American Journal of Obstetrics & Gynecology, 201*(1), 28e21-28e28.

Gardosi, J., & Francis, A. (2009b). A customized standard to assess fetal growth in a US population. *American Journal of Obstetrics & Gynecology, 201*(1), 25.e21-27.

Gardosi, J., & Francis, A. (2012). *GROW documentation*. Birmingham: Perinatal Institute. Retrieved from https://www.gestation.net/literature.htm

Gardosi, J., Mongelli, M., Wilcox, M., & Chang, A. (1995). An adjustable fetal weight standard. *Ultrasound in Obstetrics & Gynecology, 6*(3), 168-174.

Groom, K. M., North, R. A., Poppe, K. K., Sadler, L., & McCowan, L. M. E. (2007). The association between customised small for gestational age infants and pre-eclampsia or gestational hypertension varies with gestation at delivery. *BJOG: An International Journal of Obstetrics & Gynaecology, 114*(4), 478-484.

Hadlock, F. P., Harrist, R. B., & Martinez-Poyer, J. (1991). In utero analysis of fetal growth: a sonographic weight standard. *Radiology, 181*(1), 129-133.

Hemming, K., Hutton, J. L., & Bonellie, S. (2009). A comparison of customized and population-based birth-weight standards: the influence of gestational age. *European Journal of Obstetrics, Gynecology, & Reproductive Biology, 146*(1), 41-45.

Hoffman, L., Nolan, C., Wilson, J. D., Oats, J. J., & Simmons, D. (1998). Gestational diabetes mellitus--management guidelines. The Australasian Diabetes in Pregnancy Society (updated Dec 2002). *Medical Journal of Australia, 169*(2), 93-97.

Hutcheon, J. A., Zhang, X., Cnattingius, S., Kramer, M. S., & Platt, R. W. (2008). Customised birthweight percentiles: does adjusting for maternal characteristics matter? *BJOG: An International Journal of Obstetrics & Gynaecology, 115*(11), 1397-1404.

Hutcheon, J. A., Zhang, X., Platt, R. W., Cnattingius, S., & Kramer, M. S. (2011). The case against customised birthweight standards. *Paediatric and Perinatal Epidemiology, 25*(1), 11-16.

Larkin, J. C. M. D., Hill, L. M. M. D., Speer, P. D. M. D., & Simhan, H. N. M. D. (2012). Risk of Morbid Perinatal Outcomes in Small-for-Gestational-Age Pregnancies: Customized Compared With Conventional Standards of Fetal Growth. *Obstetrics & Gynecology, 119*(1), 21-27.

McCormack, R. A., Doherty, D. A., Magann, E. F., Hutchinson, M., & Newnham, J. P. (2008). Antepartum bleeding of unknown origin in the second half of pregnancy and pregnancy outcomes. *BJOG: An International Journal of Obstetrics & Gynaecology, 115*(11), 1451-1457.

McCowan, L. M. E., Dekker, G. A., Chan, E., Stewart, A. W., Chappell, L. C., Hunter, M., . . . on behalf of the SCOPE consortium. (2009). Spontaneous preterm birth and small for gestational age infants in women who stop smoking early in pregnancy: prospective cohort study.[Erratum appears in BMJ. 2009;338. doi: 10.1136/bmj.b1558]. *BMJ, 338*, b1081.

McCowan, L. M. E., Harding, J. E., & Stewart, A. W. (2005). Customised birthweight centiles predict SGA pregnancies with perinatal morbidity. *BJOG: An International Journal of Obstetrics & Gynaecology, 112*(8), 1026-1033.

McCowan, L. M. E., Stewart, A. W., Francis, A., & Gardosi, J. (2004). A customised birthweight centile calculator developed for a New Zealand population. *Australian & New Zealand Journal of Obstetrics & Gynaecology, 44*(5), 428-431.

Mikolajczyk, R. T., Zhang, J., Betran, A. P., Souza, J. P., Mori, R., Gulmezoglu, A. M., & Merialdi, M. (2011). A global reference for fetal-weight and birthweight percentiles. *Lancet, 377*(9780), 1855-1861.

Ministry of Health. (2004). *Ethnicity Data Protocols for the Health and Disability Sector*. Wellington: Ministry of Health. Retrieved from http://www.nzhis.govt.nz/documentation/ethnicity/index.html

Morken, N. H., Kallen, K., & Jacobsson, B. (2006). Fetal growth and onset of delivery: a nationwide population-based study of preterm infants. *American Journal of Obstetrics & Gynecology, 195*(1), 154-161.

National Women's Health, A. D. H. B. (2010). *National Women's Annual Clinical Report 2009*. Auckland, New Zealand: National Women's Health, Auckland District Health Board. Retrieved from http://www.adhb.govt.nz/nwhealthinfo

Rockhill, B., Newman, B., & Weinberg, C. (1998). Use and misuse of population attributable fractions.[Erratum appears in Am J Public Health. 2008 Dec;98(12):2119]. *American Journal of Public Health, 88*(1), 15-19.

Thompson, J. M., Mitchell, E. A., & Borman, B. (1994). Sex specific birthweight percentiles by gestational age for New Zealand. *New Zealand Medical Journal, 107*(970), 1-3.

Zeitlin, J., Ancel, P. Y., Saurel-Cubizolles, M. J., & Papiernik, E. (2000). The relationship between intrauterine growth restriction and preterm delivery: an empirical approach using data from a European case-control study. *BJOG, 107*(6), 750-758.

Zhang, J., Mikolajczyk, R., Grewal, J., Neta, G., & Klebanoff, M. (2011). Prenatal application of the individualized fetal growth reference. *American Journal of Epidemiology, 173*(5), 539-543.

Zhang, X., Platt, R. W., Cnattingius, S., Joseph, K. S., & Kramer, M. S. (2007). The use of customised versus population-based birthweight standards in predicting perinatal mortality. *BJOG: An International Journal Of Obstetrics And Gynaecology, 114*(4), 474-477.

Chapter 7. | Independent risk factors for customised small for gestational age infants

7.1. Preamble

The manuscript reproduced below was published online in The Australian and New Zealand Journal of Obstetrics and Gynaecology (ANZJOG) on 7th November 2012.

Permission

Reproduced from: Anderson N H, Sadler L C, Stewart A W, McCowan L M E. *Independent risk factors for infants who are small for gestational age by customised birthweight centiles in a multi-ethnic New Zealand population*. Australian & New Zealand Journal of Obstetrics & Gynaecology, 2013; 53(2)136–142.

Received 3 May 2012; accepted 20 Sept 2012.

7.2. Manuscript: Independent risk factors for customised small for gestational age infants

Abstract

Background: Infants born small for gestational age (SGA) by customised birthweight centiles are at increased risk of adverse outcomes compared with those SGA by population centiles. Risk factors for customised SGA have not previously been described in a general obstetric population.
Aim: To determine independent risk factors for customised SGA in a multi-ethnic New Zealand population.
Methods: We performed a retrospective cohort analysis of prospectively recorded maternity data from 2006 to 2009 at National Women's Health, Auckland, New Zealand. After exclusion of infants with congenital anomalies and missing data, our final study population was 26 254 singleton pregnancies. Multivariable logistic regression analysis adjusted for ethnicity, body mass index, maternal age, parity, smoking status, social deprivation, hypertensive disease, antepartum haemorrhage (APH), diabetes and relevant pre-existing medical conditions.
Results: Independent risk factors for SGA included obesity (adjusted odds ratio 1.24 [95% CI 1.11–1.39] relative to normal weight), maternal age ≥35 years (1.16 [1.05-1.30] relative to 20–29 years), nulliparity (1.13 [1.04–1.24] relative to parity 1), cigarette smoking (2.01 [1.79–2.27]), gestational hypertension (1.46 [1.21–1.75]), pre-eclampsia (2.94 [2.49–3.48]), chronic hypertension (1.68 [1.34–2.09]), placental abruption (2.57 [1.74–3.78]) and APH of unknown

origin (1.71 [1.45–2.00]). Gestational diabetes (0.80 [0.67–0.96]) and type 1 diabetes (0.26 [0.11–0.64]) were associated with reduced risk.

Conclusions: We report independent pregnancy risk factors for customised SGA in a general obstetric population. In contrast to population SGA, obesity is associated with increased risk. Our findings may help identify pregnancies that require increased fetal growth surveillance.

Introduction

Small for gestational age infants (SGA) infants are at increased risk of perinatal morbidity and mortality (Gardosi & Francis, 2009; L. M. E. McCowan, Harding, & Stewart, 2005), and survivors are at increased risk of adult cardiovascular disease, diabetes and all-cause mortality (Risnes et al., 2011). SGA has traditionally been defined as a birthweight less than the 10th population centile. However, population birthweight references are typically derived from European births that predate the obesity epidemic (Thompson, Mitchell, & Borman, 1994; Zhang & Bowes, 1995). As a result, rates of SGA by population centiles may be underestimated in obese women and overestimated in women of short stature, including women of Asian ethnicity (Gardosi, Clausson, & Francis, 2009; Thomas, Peabody, Turnier, & Clark, 2000). Additionally, population birthweight references underestimate rates of SGA infants at preterm gestations due to the association between fetal growth restriction and preterm birth (Morken, Kallen, & Jacobsson, 2006).

Birthweight customisation accounts for known physiological influences on birthweight, including ethnicity, parity and maternal height and weight (Gardosi, Mongelli, Wilcox, & Chang, 1995). Infants born SGA by customised birthweight centiles (birthweight less than the 10th customised centile) have an increased risk of adverse perinatal events compared with infants who are SGA by population centiles (Gardosi & Francis, 2009; L. M. E. McCowan et al., 2005).

Despite the increased perinatal morbidity and mortality associated with SGA, in practice fewer than half of all SGA babies in low-risk antenatal populations are currently identified prior to birth (Gardosi & Francis, 1999; Hepburn & Rosenberg, 1986; Lindqvist & Molin, 2005). Early identification of SGA has been shown to reduce perinatal morbidity and mortality (Lindqvist & Molin, 2005), and reliable identification of women at high risk would allow clinicians to monitor fetal growth and arrange timely delivery as appropriate. Previously described risk factors for SGA by population centiles include short stature, low body mass index (BMI), cigarette smoking, hypertensive diseases and Asian and Māori ethnicity (Kramer, 1987; Mantell, Craig, Stewart, Ekeroma, & Mitchell, 2004; L.M.E. McCowan & Horgan, 2009). However, obesity has usually been found to be protective for SGA when defined by population centiles (Kramer, 1987; Kramer, Platt, Yang, McNamara, & Usher, 1999; Thompson et al., 2001). One previous study in a general obstetric population has reported obesity as a risk factor for customised SGA (adjusted for a

limited number of clinical factors) (McIntyre, Gibbons, Flenady, & Callaway, 2012), while risk factors for SGA infants by customised centiles have only been previously reported in a healthy, nulliparous cohort which may not be generalisable to a general population (L.M.E. McCowan et al., 2010).

In our multi-ethnic, mixed parity general obstetric population, our primary aim was to identify independent risk factors for infants who were SGA by customised birthweight centiles. We hypothesised that after adjustment for confounding, maternal obesity would not be protective of SGA by customised centiles.

Materials and Methods

National Women's Health (NWH) is a tertiary referral service at Auckland City Hospital, Auckland, New Zealand, with a diverse ethnic population and approximately 7500 maternities per year. The NWH clinical database of births from 2006 to 2009 was used for this study. This database consists of de-identified, prospectively collected maternity data for all births occurring at ≥ 20 weeks of gestation, which includes demographic data, antenatal complications, and detailed delivery and newborn data. Data are routinely checked for completeness, out of range values and inconsistency (National Women's Health, 2012). Ethical approval for this study was gained from the Northern X Regional Ethics Committee (NTX/09/179/EXP).

Included in the study were women with singleton pregnancies delivered at NWH from January 2006 to December 2009, *n* = 29 573. After exclusion of infants with major congenital anomalies (*n* = 415) and women with missing data for maternal height and/or weight (*n* = 2901) or infant birthweight (*n* = 3), the final study population comprised 26 254 women, Figure 7.1.

Customised birthweight centiles, which were generated after birth, adjusted for maternal physiological factors (ethnicity, height, weight and parity) and infant gender (Anderson, Sadler, Stewart, & McCowan, 2012; Gardosi et al., 1995). Variables considered *a priori* risk or protective factors for SGA were as follows: ethnicity, ethnic-specific BMI, maternal age, parity, smoking status, socio-economic status, hypertensive disease, diabetes, antepartum haemorrhage (APH) and pre-existing medical conditions known to be associated with fetal growth restriction.

Ethnicity was self-determined and prioritised as per New Zealand Ministry of Health guidelines (Ministry of Health, 2004). Other Asian ethnicity included women from South-East Asia and the Indian subcontinent (excluding India).

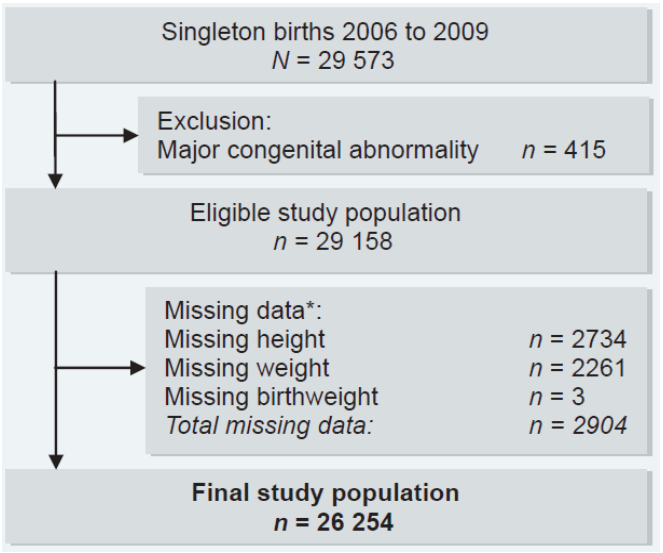


Figure 7.1. Flow chart of participants
***Data may be missing for >1 variable, so numbers do not total**

Maternal height and weight were recorded at the first antenatal booking visit and measured to the nearest centimetre and kilogram, respectively. Women were classified into normal, overweight and obese groups according to ethnic-specific BMI criteria (World Health Organization expert consultation, 2004). This classification accounts for differing body fat and muscle masses between ethnicities, resulting in lower BMI criteria for overweight and obesity in Asian/Indian women (normal 18.5–22.9 kg/m^2, overweight 23–27.4 kg/m^2 and obese ≥27.5 kg/m^2) and higher BMI criteria for overweight and obesity in Pacific and Māori women (normal 18.5–25.9 kg/m^2, overweight 26–31.9 kg/m^2 and obese ≥32 kg/m^2). For European women and women of all other ethnicities, standard World Health Organization (WHO) criteria were used (normal 18.5–24.9 kg/m^2, overweight 25–29.9 kg/m^2 and obese ≥30 kg/ m^2) (World Health Organization, 2000).

Parity was defined as the number of times a woman had given birth to liveborn or stillborn infant(s) of any birthweight from 20 weeks of gestation, or if gestation was unknown, where the infant weighed ≥ 400g (Bai, Wong, Bauman, & Mohsin, 2002). Cigarette smoking status was recorded both at booking and at delivery. If a woman was smoking at either time point she was defined as a smoker for the purposes of this study. Socio-economic status was estimated using a centile score (range 1–10) based on residential area deprivation data from the 2006 New Zealand census (NZDep2006) (Salmond, Crampton, & Atkinson, 2007). Centile scores were condensed into quintiles (range 1–5) where quintile 1 represented the least deprived residential areas and deprivation quintile 5 the most deprived areas.

Chronic hypertension, gestational hypertension and pre-eclampsia were defined by the International Society for the Study of Hypertension in Pregnancy guidelines (Brown, Lindheimer, de Swiet, Van Assche, & Moutquin, 2001). Those women with chronic hypertension

who developed pre-eclampsia were categorised separately as superimposed pre-eclampsia. Diabetes was classified into a pre-pregnancy diagnosis of diabetes (type 1 or type 2 diabetes mellitus), gestational diabetes mellitus (GDM) or unknown diabetes status. GDM was diagnosed using the Australasian Diabetes in Pregnancy Society guidelines (Hoffman, Nolan, Wilson, Oats, & Simmons, 1998). APH of unknown origin was defined as vaginal bleeding from any cause at or beyond 20 weeks of gestation after excluding known causes such as lower genital tract bleeding, placenta praevia, vasa praevia and abruption. Abruption was only diagnosed where a retroplacental clot was seen on ultrasound or at delivery (National Women's Health, 2012). Pre-existing medical conditions included antiphospholipid syndrome, renal disease and systemic lupus erythematosus (L.M.E. McCowan & Horgan, 2009).

Statistical Methods

Univariable analysis of categorical data was performed using the chi-square test, and continuous data were compared using Student's *t*-test assuming equality of variance. A *P*-value < 0.05 was considered significant. Crude and adjusted odds ratios (OR and aOR) with 95% CI were calculated using simple and multivariable logistic regression, with all *a priori* variables included in the multivariable logistic regression model. Referent groups for pathological variables (smoking status, hypertensive disease, diabetes, APH and pre-existing medical conditions) were those women without the respective pathology, and all other referent groups are indicated in Table 7.1. All statistical tests were performed using SAS© version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

Infants who were SGA by customised birthweight centiles comprised 11.8% (*n* = 3087) of the study population. Characteristics of the study population by SGA status are presented in Table 7.1 and late pregnancy outcomes by SGA status are presented in Table 7.2. Of note, 84.7% (*n* = 2614) of SGA infants were delivered at term (≥37 weeks of gestation).

Crude odds for customised SGA were elevated in Māori (OR 1.37, 95% CI [1.19-1.57]) and Pacific women (OR 1.24, [1.11-1.38]), and reduced in Chinese women (OR 0.83, [0.73-0.95]) compared to European, Table 7.1. Similarly maternal BMI, parity, cigarette smoking, socio-economic deprivation, hypertensive disease, diabetes, APH and pre-existing medical conditions were associated with customised SGA after univariable analysis. Rates of SGA by customised centile increased with increasing BMI category, Figure 7.2.

Table 7.1. Characteristics of study population by small for gestational age (SGA) status, with crude and adjusted odds ratios (OR [95%CI]) for SGA

	SGA		Non-SGA		Crude	Adjusted	
	n = 3087	11.8%	*n* = 23,167	88.2%	OR [95% CI]	OR [95% CI]	*P*-value†
Maternal ethnicity							
European	1468	11.2	11,611	88.8	Ref	Ref	0.28
Māori	282	14.7	1631	85.3	1.37 [1.19–1.57]	1.04 [0.89–1.22]	
Pacific	500	13.6	3185	86.4	1.24 [1.11–1.38]	1.05 [0.92–1.20]	
Chinese	299	9.5	2849	90.5	0.83 [0.73–0.95]	0.93 [0.81–1.06]	
Indian	231	12.4	1638	87.6	1.12 [0.96–1.29]	1.15 [0.98–1.34]	
Other Asian	196	11.8	1472	88.2	1.05 [0.90–1.23]	1.09 [0.93–1.29]	
Other ethnicity	111	12.4	781	87.6	1.12 [0.92–1.38]	1.22 [0.98–1.50]	
BMI (ethnic-specific)							
Underweight	100	10.5	851	89.5	0.98 [0.79–1.22]	1.04 [0.84–1.30]	<0.01
Normal	1441	10.7	12,060	89.3	Ref	Ref	
Overweight	849	12.1	6195	87.9	1.15 [1.05–1.26]	1.07 [0.97–1.17]	
Obese	697	14.6	4061	85.4	1.44 [1.30–1.58]	1.24 [1.11–1.39]	
Maternal age (years)							
<20	110	14.0	677	86.0	1.22 [0.98–1.50]	0.99 [0.79–1.23]	0.03
20–29	989	11.8	7393	88.2	Ref	Ref	
30–34	995	11.1	7932	88.9	0.94 [0.85–1.03]	1.05 [0.95–1.16]	
≥35	993	12.2	7165	87.8	1.04 [0.94–1.14]	1.16 [1.05–1.30]	
Parity							
Nulliparous	1554	12.1	11,306	87.9	1.13 [1.04–1.24]	1.13 [1.04–1.24]	0.03
1	934	10.8	7709	89.2	Ref	Ref	
2	332	11.5	2553	88.5	1.07 [0.94–1.23]	0.99 [0.86–1.13]	
≥3	267	14.3	1599	85.7	1.38 [1.19–1.60]	1.06 [0.91–1.25]	
Smoking	498	20.1	1979	79.9	2.06 [1.85–2.29]	2.01 [1.79–2.27]	<0.01
Deprivation quintile (NZDep2006)‡							
1	504	10.7	4202	89.3	Ref	Ref	0.30
2	587	11.4	4573	88.6	1.07 [0.94–1.21]	1.04 [0.91–1.18]	
3	647	11.5	4986	88.5	1.08 [0.96–1.22]	1.03 [0.90–1.16]	
4	717	12.8	4891	87.2	1.22 [1.08–1.38]	1.10 [0.96–1.25]	
5	628	12.2	4506	87.8	1.16 [1.03–1.32]	0.97 [0.84–1.11]	
Hypertensive disease							
Gestational hypertension	149	15.5	814	84.5	1.50 [1.26–1.80]	1.46 [1.21–1.75]	<0.01
Pre-eclampsia (PE)	211	27.7	551	72.3	3.15 [2.67–3.71]	2.94 [2.49–3.48]	
Chronic hypertension	102	17.7	475	82.3	1.76 [1.42–2.19]	1.68 [1.34–2.09]	
Superimposed PE§	36	37.9	59	62.1	5.01 [3.31–7.61]	4.49 [2.94–6.88]	
No hypertensive disease	2589	10.9	21,268	89.1	Ref	Ref	
Diabetes							
Gestational	154	10.6	1296	89.4	0.95 [0.80–1.13]	0.80 [0.67–0.96]	<0.01
Type 1	5	4.0	120	96.0	0.33 [0.14–0.81]	0.26 [0.11–0.64]	
Type 2	41	18.3	183	81.7	1.79 [1.27–2.52]	1.11 [0.78–1.59]	
Unknown	877	13.8	5496	86.2	1.28 [1.17–1.39]	1.24 [1.14–1.35]	
No diabetes	2010	11.1	16,072	88.9	Ref	Ref	
Antepartum haemorrhage							
Abruption	39	29.1	95	70.9	3.20 [2.20–4.66]	2.57 [1.74–3.78]	<0.01
Unknown origin	203	18.8	875	81.2	1.81 [1.55–2.12]	1.71 [1.45–2.00]	
No APH	2845	11.4	22,197	88.6	Ref	Ref	
Pre-existing medical¶	41	17.3	196	82.7	1.58 [1.12–2.21]	1.45 [1.02–2.06]	0.04

BMI, body mass index; APH, antepartum haemorrhage.
Data presented are *n* % and OR [95% CI] as appropriate.
Adjusted ORs are adjusted for all variables in the table.
†Chi-square P-value for adjusted model.
‡*n* = 13 missing data.
§Pre-eclampsia superimposed on chronic hypertension.
¶Pre-existing medical conditions; renal disease, antiphospholipid syndrome, systemic lupus erythematosus.

Independent risk factors for customised SGA were obesity, nulliparity, cigarette smoking, hypertensive diseases, unknown diabetes status, APH and pre-existing medical conditions, Table 7.1. A reduced risk of customised SGA was seen in women with GDM and type 1 diabetes. For completeness, multivariable analysis was also performed using standard WHO BMI criteria, and no change in statistical significance was observed (data not presented).

Table 7.2. Late pregnancy outcomes by SGA status

	SGA *n* = 3087		Non-SGA *n* = 23,167	
Gestation at delivery (weeks)	38.1	(3.5)	39.0	(1.9)
Pre-term birth (<37 weeks)	473	(15.3%)	1308	(5.6%)
Birthweight (g)	2628	(605)	3507	(514)
Stillbirth†	92	(29.8)	61	(2.6)
Neonatal death†	24	(7.8)	29	(1.3)

SGA, small for gestational age.
Data presented are *n* %, mean (SD) as appropriate.
All *P*-values <0.01.
†Stillbirth and neonatal death (to one month after birth) rate per 1000 total births

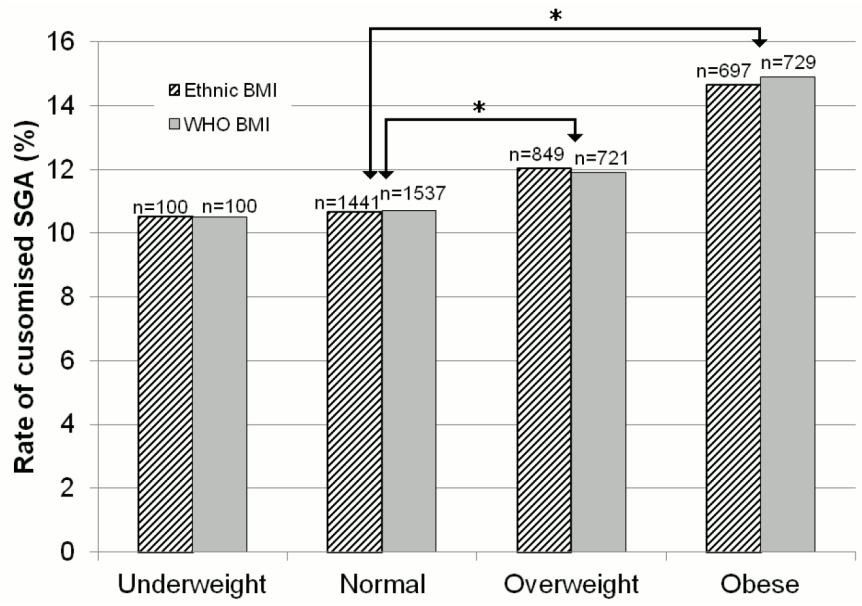


Figure 7.2. Rates of customised small for gestational age infants (SGA) by ethnic specific and World Health Organization (WHO) body mass index categories.
*** *P* <0.01 for differences between normal and overweight or obese categories for both ethnic-specific and WHO BMI classifications**

Discussion

In a multi-ethnic general obstetric population, we have identified the following independent risk factors for infants SGA by customised birthweight centiles: obesity, increasing maternal age, nulliparity, cigarette smoking, hypertensive disease, APH and pre-existing medical conditions. Type 1 diabetes and GDM were found to reduce the risk of SGA. Consistent with our hypothesis, maternal obesity was not protective of customised SGA, but instead was found to have a 24% increase in risk compared to women of normal weight.

As 70% of small babies are SGA by both customised and population criteria (L. M. E. McCowan et al., 2005), it is expected that there will be considerable overlap in risk factors, however only one previous study has investigated specific risk factors for SGA by customised centiles (L.M.E. McCowan et al., 2010). Direct comparisons with this previous study are limited as it was performed in a healthy nulliparous cohort where women with pre-existing medical disorders were excluded and only risk factors present in early pregnancy were reported. However, cigarette smoking and increasing maternal age were common risk factors in the two studies. Cigarette smoking is an important modifiable risk factor as cessation of smoking in early pregnancy reduces the risk of SGA and is an important goal of antenatal care (L.M.E. McCowan et al., 2009).

Customised birthweight centiles compare actual birthweight to an ideal gestation-matched birthweight adjusted for the maternal physiological factors known to influence birthweight (height, weight, parity and ethnicity) (Gardosi et al., 1995). In addition, the optimal referent standard excludes known pathological influences on birthweight, in particular, smoking, hypertensive disease, diabetes and APH. Therefore, any independent associations between customised SGA and maternal factors (e.g. obesity) are over-and-above the normal physiological associations with birthweight, and prior knowledge of the effect of maternal pathologies on birthweight means an association with customised SGA is expected.

In our multi-ethnic, general obstetric population, obesity was an independent and, from a population perspective, clinically important risk factor for customised SGA (aOR 1.24 [1.11–1.39]). For completeness, multivariable analysis was also performed using standard WHO BMI criteria and obesity remained independently associated with customised SGA (aOR 1.26 [1.12–1.41]). Few previous studies have investigated obesity and customised SGA. Previous studies using population birthweight centiles have reported obesity as either having no impact on risk, or being protective of SGA (Kramer et al., 1999; Thompson et al., 2001). Consistent with our findings, a recent multivariable analysis of pregnancy complications associated with obesity in a general obstetric population also showed maternal obesity to be associated with an increased risk of customised SGA, despite only being able to adjust for a limited number of clinical

variables (McIntyre et al., 2012). A further study reported increased rates of customised SGA with increasing maternal BMI but did not adjust for confounders (Gardosi et al., 2009). The only previous multivariable analysis of risk factors for infants SGA by customised centiles did not find an independent association between BMI and SGA in a low-risk nulliparous cohort (L.M.E. McCowan et al., 2010). Our finding of an association between obesity and SGA in a general obstetric population raises particular challenges as SGA is less likely to be detected antenatally in obese women (Williams, Southam, & Gardosi, 2010).

Nulliparous women also had an increased risk of customised SGA (aOR 1.13 [1.04-1.24]). This is consistent with the well established association between nulliparity and SGA by population centiles (Gardosi et al., 2009; Kramer, 1987; Kramer et al., 1999; Thompson et al., 2001).

Population birthweight references do not account for the substantial differences in physiological determinants of birthweight that may occur between ethnicities (Anderson et al., 2012; Gardosi et al., 1995; L.M.E. McCowan & Horgan, 2009), and by not adjusting for these known birthweight influences, population centiles can overestimate or underestimate an association between SGA and ethnicity (Kramer, 1987; Thompson et al., 2001). In the present analyses although increased rates of customised SGA were initially observed in Māori and Pacific women on univariable analysis, this was fully accounted for on multivariable analysis by factors such as cigarette smoking, hypertensive disease, diabetes and obesity.

Studies using population birthweight references have variably reported socio-economic status as both a risk factor for (Elo et al., 2009), and having no association with population SGA (Kramer, 1987; Kramer et al., 1999; Thompson et al., 2001). The initial univariable association seen in our analyses between low socio-economic status and customised SGA did not remain after adjustment for known confounding factors, indicating that the association with socio-economic status can be explained by factors such as high smoking rates and obesity in deprived areas.

Consistent with findings from studies that have defined SGA by population centiles, all types of hypertensive disease were independent risk factors for customised SGA (Kramer, 1987; L.M.E. McCowan & Horgan, 2009). The greatest risk was seen in women with pre-eclampsia superimposed on chronic hypertension who had a 4.5-fold increase in risk. Of note gestational hypertension, which occurred in 3.7% (n = 963) of the cohort, carried a nearly 50% increase in risk of SGA, and women with APH of unknown origin (n = 1078, 4.1%) had a 70% increase in risk. Consistent with a previous study, we also found the vast majority of SGA infants (84.7%) were delivered at term (Groom, North, Poppe, Sadler, & McCowan, 2007). Our findings together suggest that additional surveillance for fetal growth should be undertaken in the presence of hypertensive and bleeding complications and that surveillance should be continued until delivery.

Fetal growth in women with diabetes in pregnancy correlates both with the degree of glycaemic control and presence or absence of vasculopathy (Reece et al., 1990). Our study showed both GDM and type 1 diabetes were protective for SGA. Small numbers of women with type 1 diabetes means results from this group need to be interpreted with caution. Women with type 2 diabetes, who on univariable analysis had a nearly 70% increased risk of SGA, did not have an increased risk after multivariable analysis. However we observed an increased risk of customised SGA in women with unknown diabetes status (*n* = 6373, 24%; aOR 1.24 [1.14-1.35]). In the NWH clinical database, women with unknown diabetes status are a heterogenous group who were either not screened (including women who have poor antenatal attendance or who booked late in gestation) or were screen negative and this information was not recorded. Women who have poor antenatal attendance or book late in gestation are more likely to have additional risk factors for SGA, such as cardiac disease, substance abuse or other obstetric risk factors such as previous stillbirth or preterm birth (Kupek, Petrou, Vause, & Maresh, 2002). Risk factors such as these that were not able to be included in the current model will partly explain the increased risk of SGA seen in women with unknown diabetes status.

A limitation of this study was that the analysis was performed using a retrospective hospital database, albeit with robust data cleaning. Factors that other investigators have reported to be associated with SGA such as low gestational weight gain (Rasmussen & Yaktine, 2009) and low maternal birthweight (L.M.E. McCowan & Horgan, 2009) were not able to be included as they were not recorded in this database.

Additionally, the majority of the cohort used for the current SGA analysis were also used to create the coefficients for the New Zealand customised birthweight centile calculator (*n*=24 176, 92.1%) (Anderson et al., 2012). Our findings should therefore be confirmed in a large independent multiethnic general obstetric cohort, and we intend to repeat these analyses when we have a sufficiently large independent sample.

Conclusion

We report independent early and late pregnancy risk factors for customised SGA infants in a multi-ethnic, mixed parity population. In contrast to studies of risk factors for infants SGA by population centiles, obesity is not protective but is independently associated with increased risk of customised SGA. Our findings may assist clinicians to stratify risk for customised SGA infants in clinical practice to identify pregnancies that require increased fetal growth surveillance.

References

Anderson, N., Sadler, L., Stewart, A., & McCowan, L. (2012). Maternal and pathological pregnancy characteristics in customised birthweight centiles and identification of at-risk small-for-gestational-age infants: a retrospective cohort study. *BJOG, 119*(7), 848-856.

Bai, J., Wong, F. W., Bauman, A., & Mohsin, M. (2002). Parity and pregnancy outcomes. *American Journal of Obstetrics & Gynecology, 186*(2), 274-278.

Brown, M. A., Lindheimer, M. D., de Swiet, M., Van Assche, A., & Moutquin, J. M. (2001). The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). *Hypertension in Pregnancy, 20*(1), IX-XIV.

Elo, I. T., Culhane, J. F., Kohler, I. V., O'Campo, P., Burke, J. G., Messer, L. C., . . . Holzman, C. (2009). Neighbourhood deprivation and small-for-gestational-age term births in the United States. *Paediatric and Perinatal Epidemiology, 23*(1), 87-96.

Gardosi, J., Clausson, B., & Francis, A. (2009). The value of customised centiles in assessing perinatal mortality risk associated with parity and maternal size. *BJOG: An International Journal of Obstetrics & Gynaecology, 116*(10), 1356-1363.

Gardosi, J., & Francis, A. (1999). Controlled trial of fundal height measurement plotted on customised antenatal growth charts. *British Journal of Obstetrics & Gynaecology, 106*(4), 309-317.

Gardosi, J., & Francis, A. (2009). Adverse pregnancy outcome and association with small for gestational age birthweight by customized and population-based percentiles. *American Journal of Obstetrics & Gynecology, 201*(1), 28e21-28e28.

Gardosi, J., Mongelli, M., Wilcox, M., & Chang, A. (1995). An adjustable fetal weight standard. *Ultrasound in Obstetrics & Gynecology, 6*(3), 168-174.

Groom, K. M., North, R. A., Poppe, K. K., Sadler, L., & McCowan, L. M. E. (2007). The association between customised small for gestational age infants and pre-eclampsia or gestational hypertension varies with gestation at delivery. *BJOG: An International Journal of Obstetrics & Gynaecology, 114*(4), 478-484.

Hepburn, M., & Rosenberg, K. (1986). An audit of the detection and management of small-for-gestational age babies. *British Journal of Obstetrics & Gynaecology, 93*(3), 212-216.

Hoffman, L., Nolan, C., Wilson, J. D., Oats, J. J., & Simmons, D. (1998). Gestational diabetes mellitus--management guidelines. The Australasian Diabetes in Pregnancy Society (updated Dec 2002). *Medical Journal of Australia, 169*(2), 93-97.

Kramer, M. S. (1987). Determinants of low birth weight: methodological assessment and meta-analysis. *Bulletin of the World Health Organization, 65*(5), 663-737.

Kramer, M. S., Platt, R., Yang, H., McNamara, H., & Usher, R. H. (1999). Are all growth-restricted newborns created equal(ly)? *Pediatrics, 103*(3), 599-602.

Kupek, E., Petrou, S., Vause, S., & Maresh, M. (2002). Clinical, provider and sociodemographic predictors of late initiation of antenatal care in England and Wales. *BJOG: An International Journal of Obstetrics & Gynaecology, 109*(3), 265-273.

Lindqvist, P. G., & Molin, J. (2005). Does antenatal identification of small-for-gestational age fetuses significantly improve their outcome? *Ultrasound in Obstetrics & Gynecology, 25*(3), 258-264.

Mantell, C. D., Craig, E. D., Stewart, A. W., Ekeroma, A. J., & Mitchell, E. A. (2004). Ethnicity and birth outcome: New Zealand trends 1980-2001: Part 2. Pregnancy outcomes for Maori women. *Australian & New Zealand Journal of Obstetrics & Gynaecology, 44*(6), 537-540.

McCowan, L. M. E., Dekker, G. A., Chan, E., Stewart, A. W., Chappell, L. C., Hunter, M., . . . on behalf of the SCOPE consortium. (2009). Spontaneous preterm birth and small for gestational age infants in women who stop smoking early in pregnancy: prospective cohort study.[Erratum appears in BMJ. 2009;338. doi: 10.1136/bmj.b1558]. *BMJ, 338*, b1081.

McCowan, L. M. E., Harding, J. E., & Stewart, A. W. (2005). Customised birthweight centiles predict SGA pregnancies with perinatal morbidity. *BJOG: An International Journal of Obstetrics & Gynaecology, 112*(8), 1026-1033.

McCowan, L. M. E., & Horgan, R. P. (2009). Risk factors for small for gestational age infants. *Best Practice & Research in Clinical Obstetrics & Gynaecology, 23*(6), 779-793.

McCowan, L. M. E., Roberts, C. T., Dekker, G. A., Taylor, R. S., Chan, E. H., Kenny, L. C., . . . on behalf of the SCOPE consortium. (2010). Risk factors for small-for-gestational-age infants by customised birthweight centiles: data from an international prospective cohort study. *BJOG, 117*(13), 1599-1607.

McIntyre, H. D., Gibbons, K. S., Flenady, V. J., & Callaway, L. K. (2012). Overweight and obesity in Australian mothers: epidemic or endemic? *Medical Journal of Australia, 196*(3), 184-188.

Ministry of Health. (2004). *Ethnicity Data Protocols for the Health and Disability Sector*. Wellington: Ministry of Health. Retrieved from http://www.nzhis.govt.nz/documentation/ethnicity/index.html

Morken, N. H., Kallen, K., & Jacobsson, B. (2006). Fetal growth and onset of delivery: a nationwide population-based study of preterm infants. *American Journal of Obstetrics & Gynecology, 195*(1), 154-161.

National Women's Health, A. D. H. B. (2012). *National Women's Annual Clinical Report 2011*. Auckland, New Zealand: National Women's Health, Auckland District Health Board. Retrieved from http://www.adhb.govt.nz/nwhealthinfo

Rasmussen, K. M., & Yaktine, A. L. (Eds.). (2009). *Weight Gain During Pregnancy: Reexamining the Guidelines*. Washington, D.C.: National Academies Press.

Reece, E. A., Smikle, C., O'Connor, T. Z., Holford, T., Nelson-Robinson, L., Degennaro, N., & Hobbins, J. C. (1990). A longitudinal study comparing growth in diabetic pregnancies with growth in normal gestations: I. The fetal weight. *Obstet Gynecol Surv, 45*(3), 161-164.

Risnes, K., Vatten, L., Baker, J., Jameson, K., Sovio, U., Kajantie, E., . . . Bracken, M. (2011). Birthweight and mortality in adulthood: a systematic review and meta-analysis. *Int J Epidemiol., 40*(3), 647-661. Epub 2011 Feb 2015.

Salmond, C., Crampton, P., & Atkinson, J. (2007). *NZDep2006 Index of Deprivation*. Wellington: University of Otago.

Thomas, P., Peabody, J., Turnier, V., & Clark, R. H. (2000). A new look at intrauterine growth and the impact of race, altitude, and gender. *Pediatrics, 106*(2), E21.

Thompson, J. M., Clark, P. M., Robinson, E., Becroft, D. M., Pattison, N. S., Glavish, N., . . . Mitchell, E. A. (2001). Risk factors for small-for-gestational-age babies: The Auckland Birthweight Collaborative Study. *Journal of Paediatrics & Child Health, 37*(4), 369-375.

Thompson, J. M., Mitchell, E. A., & Borman, B. (1994). Sex specific birthweight percentiles by gestational age for New Zealand. *New Zealand Medical Journal, 107*(970), 1-3.

Williams, M., Southam, M., & Gardosi, J. (2010). Antenatal detection of fetal growth restriction and stillbirth risk in mothers with high and low body mass index. *Archives of Disease in Childhood Fetal & Neonatal Edition, 95*, Fa92.

World Health Organization. (2000). *Obesity: Preventing and Managing the Global Epidemic: report of a WHO Consultation* (WHO Technical Report Series 894). Geneva, Switzerland: World Health Organisation.

World Health Organization expert consultation. (2004). Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet, 363*(9403), 157-163.

Zhang, J., & Bowes, W. A., Jr. (1995). Birth-weight-for-gestational-age patterns by race, sex, and parity in the United States population. *Obstetrics & Gynecology, 86*(2), 200-208.

Chapter 8. | The phenotype of pre-eclampsia in overweight and obese women

8.1. Preamble

The manuscript reproduced below was published in the British Journal of Obstetrics and Gynaecology (BJOG) in February 2012.

Accepted 16 December 2011. Published Online 3 February 2012.

8.2. Manuscript: The phenotype of pre-eclampsia in overweight and obese women

Abstract

Objective: We hypothesised that among nulliparous women with pre-eclampsia, overweight or obese women would have a different phenotype of pre-eclampsia compared with normal weight women with pre-eclampsia. Specifically, they are more likely to develop term pre-eclampsia and less likely to have indicators of impaired placental perfusion, e.g. abnormal uterine artery Doppler or a small-for-gestational age (SGA) infant.

Design: Prospective, multicentre, cohort SCOPE study (*n* = 3170).

Setting: New Zealand and Australia.

Population: Nulliparous women who developed pre-eclampsia.

Methods: Participants were interviewed at 14–16 weeks of gestation, uterine artery Doppler studies were performed at 19–21 weeks and pregnancy outcome was tracked prospectively.

Main outcome measures: Rates of abnormal uterine artery Doppler indices, term/preterm birth and SGA infants were compared between normal, overweight and obese women with pre-eclampsia. Multivariable analysis was performed to examine the association between body mass index (BMI) and term pre-eclampsia.

Results: Of 178 women with pre-eclampsia, one underweight woman was excluded and 66 (37%) were normal weight, 52 (29%) were overweight and 59 (34%) obese. Pre-eclampsia developed preterm in 26% of women and at term in 74% of women. There were no differences

in the rates of term/preterm pre-eclampsia, abnormal uterine artery Doppler indices or SGA infants between BMI groups (P >0.10). No independent association between BMI and term pre-eclampsia was found (P = 0.56).

Conclusions: Among women with pre-eclampsia, those who are overweight or obese in early pregnancy are not more likely to have term pre-eclampsia compared to women with a normal BMI. Overweight and obese women require vigilant surveillance for the development of preterm as well as term pre-eclampsia.

Introduction

Pre-eclampsia, which affects up to 7% of nulliparous women, is a major cause of maternal and perinatal morbidity and mortality globally (B. Sibai, Dekker, & Kupferminc, 2005). It is widely recognised that there are sub-phenotypes of pre-eclampsia (Huppertz, 2008; von Dadelszen, Magee, & Roberts, 2003). Pre-eclampsia arising preterm is typified by the presence of defective trophoblast remodelling of the uterine spiral arteries and secondary fetal growth restriction (K. M. Groom, North, Poppe, Sadler, & McCowan, 2007; Huppertz, 2008; von Dadelszen et al., 2003). In contrast, term pre-eclampsia is usually associated with normal utero-placental blood flow (as indicated by normal uterine artery Doppler waveforms) and normal fetal growth, and is thought to result largely from an exaggerated maternal response to pregnancy (Huppertz, 2008; Vatten & Skjaerven, 2004).

Maternal obesity predisposes a woman to developing pre-eclampsia and a dose dependent relationship between increasing body mass index (BMI) and the risk of developing pre-eclampsia is well established (Mbah et al., 2010; O'Brien, Ray, & Chan, 2003). Many studies have investigated obstetric complications in obese women, but the few data reporting clinical features of pre-eclampsia associated with being overweight or obese are conflicting (Bodnar, Catov, Klebanoff, Ness, & Roberts, 2007; Mbah et al., 2010; Odegard, Vatten, Nilsen, Salvesen, & Austgulen, 2000; B. M. Sibai et al., 1997; Stone et al., 1994). Consequently the clinical phenotype of pre-eclampsia in obese women is poorly characterised. A recent retrospective cohort study of 850 000 women reported that compared with control women of normal BMI, obesity was more strongly associated with pre-eclampsia occurring at 34 weeks of gestation or beyond than pre-eclampsia before 34 weeks of gestation (Mbah et al., 2010).

In our international prospective SCOPE (Screening for Pregnancy Endpoints) study, 45% of the nulliparous participants were overweight or obese by ethnicity-specific BMI criteria (World Health Organization, 2000). We hypothesised that among women with pre-eclampsia, the phenotype of pre-eclampsia would differ by BMI. In particular, pre-eclampsia in women who were overweight or obese by ethnicity-specific BMI criteria would be more likely to occur at term and less likely to be associated with abnormal uterine artery Doppler resistance indices

(RI) or infants who were small for gestational age (SGA) by customised birthweight centiles compared with pre-eclampsia in women who had a normal BMI.

Methods

Healthy nulliparous women with singleton pregnancies were recruited to the SCOPE study between November 2004 and October 2008 in Auckland, New Zealand and Adelaide, Australia. SCOPE is a prospective, multi-centre cohort study with the main aim of developing screening tests to predict pre-eclampsia, fetal growth restriction and spontaneous preterm birth (North et al., 2011; McCowan, North, & Taylor, 2007). Ethical approval was obtained in each centre from the local ethics committees (New Zealand AKX/02/00/364, Australia REC 1712/5/2008) and all women gave written informed consent. Exclusion criteria included being at high risk of pre-eclampsia, SGA or spontaneous preterm birth because of underlying medical conditions such as chronic hypertension requiring antihypertensive therapy, diabetes, gynaecological history, or if they received interventions that may modify pregnancy outcome, e.g. low-dose aspirin (North et al., 2011).

Detailed study methods have been previously published (North et al., 2011). In brief, women were interviewed and examined at 14–16 weeks of gestation by a research midwife and details of their sociodemographic, medical, gynaecological and family history, history of medical and obstetric disorders and health in current pregnancy were obtained. Dietary and lifestyle questionnaires were completed. Maternal physical measurements obtained by a research midwife included blood pressure (two consecutive manual blood pressure measurements with mercury or aneroid sphygmomanometer, with a large cuff if the arm circumference was ≥33 cm and Korotkoff V for diastolic blood pressure), height (in cm) and weight (in kg) (North et al., 2011). The estimated date of delivery was calculated from a certain last menstrual period (LMP) date and was only adjusted if either (1) an ultrasound scan performed at less than 16 weeks of gestation found a difference of ≥7 days between the scan gestation and that calculated by the LMP or (2) on the scan at 19–21 weeks a difference of ≥10 days was found between the scan gestation and that calculated from the LMP. If an LMP date was uncertain, then scan dates were used to calculate the estimated date of delivery.

An ultrasound scan performed at 19–21 weeks of gestation included fetal growth measurements, fetal anatomy and uterine artery Doppler RI. Ultrasound examinations were performed in clinical practice by sonographers with Diplomas in Medical Ultrasound from the Australasian Society of Ultrasound in Medicine, in accordance with a standard operating procedures manual (Katie M. Groom et al., 2009). Mean uterine artery RI was calculated from the left and right uterine RI and an abnormal uterine artery Doppler result was defined as a

mean RI greater than the 90th centile for gestation for the SCOPE population (RI >0.695) (Katie M. Groom et al., 2009).

Women were followed prospectively, with pregnancy, birth and neonatal outcome data collected by research midwives from hospital records and interview usually within 72 hours of birth. These data included end of pregnancy outcomes (e.g. pre-eclampsia, SGA or spontaneous preterm birth), labour and delivery data and maternal and neonatal postpartum complications (North et al., 2011). All data were entered into an internet accessed, auditable database (Medscinet^{AB}, Stockholm, Sweden) and were monitored for accuracy and completeness.

Women were classified into normal, overweight and obese groups according to ethnicity-specific BMI criteria (WHO/IASO/IOTF, 2000). This classification accounts for differing body fat and muscle masses between ethnicities, resulting in lower BMI criteria for overweight and obesity in Asian/Indian women (normal 18.5–22.9 kg/m^2, overweight 23–27.4 kg/m^2 and obese ≥27.5 kg/m^2) and higher BMI criteria for overweight and obesity in Pacific and Māori women (normal 18.5–25.9 kg/m^2, overweight 26–31.9 kg/m^2 and obese ≥32 kg/m^2). For European women and women of all other ethnicities, standard World Health Organization (WHO) criteria were used (normal 18.5–24.9 kg/m^2, overweight 25–29.9 kg/ m^2 and obese ≥30 kg/m^2) (World Health Organization, 2000). To check the influence of ethnicity-specific BMI classification on our results, we also performed analyses with all women classified using standard WHO BMI categories.

Pre-eclampsia was defined as systolic blood pressure ≥140 mmHg and diastolic blood pressure (DBP) ≥90mmHg on at least two occasions 4 hours apart after 20 weeks of gestation but before the onset of labour, or postpartum, with either proteinuria (24-hour urinary protein ≥300 mg or spot urine protein:creatinine ratio ≥30 mg/mmol creatinine or urine dipstick protein ≥2+) or any multi-system complication of pre-eclampsia (McCowan, et al., 2007; North et al., 2011). Multi-system complications included any of: acute renal insufficiency, defined as a new increase in serum creatinine concentration ≥100 μmol/l antepartum or >130 μmol/l postpartum; effects on liver, defined as raised aspartate transaminase or alanine transaminase concentration, or both, >45 IU/l or severe right upper quadrant or epigastric pain or liver rupture; neurological effects included eclampsia, imminent eclampsia (severe headache with hyper-reflexia and persistent visual disturbance), or cerebral haemorrhage; and haematological effects included thrombocytopenia (platelets <100×10^9/l), disseminated intravascular coagulation, or haemolysis (North et al., 2011). Preterm and term pre-eclampsia was defined as pre-eclampsia resulting in delivery before 37 weeks of gestation or at 37 weeks or beyond, respectively.

SGA and large for gestational age (LGA) were defined as an infant birthweight less than the 10th and greater than the 90th customised centile respectively, adjusted for maternal height, booking

weight, parity and ethnicity as well as delivery gestation and infant sex (McCowan, Stewart, Francis, & Gardosi, 2004).

Statistical Methods

Among women with pre-eclampsia, characteristics related to pre-eclampsia phenotype (rates of abnormal uterine Doppler indices, multi-system complications, SGA infant, LGA infant and term/preterm pre-eclampsia) were compared between the three BMI categories using the chi-square test, Table 8.1. Maternal and infant characteristics were compared between term and preterm pre-eclampsia, using the chi-square test for categorical variables and the Student's *t*-test for continuous variables, Table 8.2. Kaplan-Meier survival analysis of gestation to onset of pre-eclampsia was performed with log-rank test of equality to compare groups.

A *P*-value of <0.05 was considered significant.

Multivariable logistic regression was performed to determine if BMI was associated with term pre-eclampsia, adjusting for maternal age, primigravidity, ethnicity, mean arterial blood pressure at 14–16 weeks of gestation and SGA infant. An interaction term between BMI and SGA was included in the model. Uterine Doppler indices were considered on the causal pathway and not included in the model.

All statistical tests were performed using SAS ® version 9.1 (SAS Institute Inc., Cary, NC, USA).

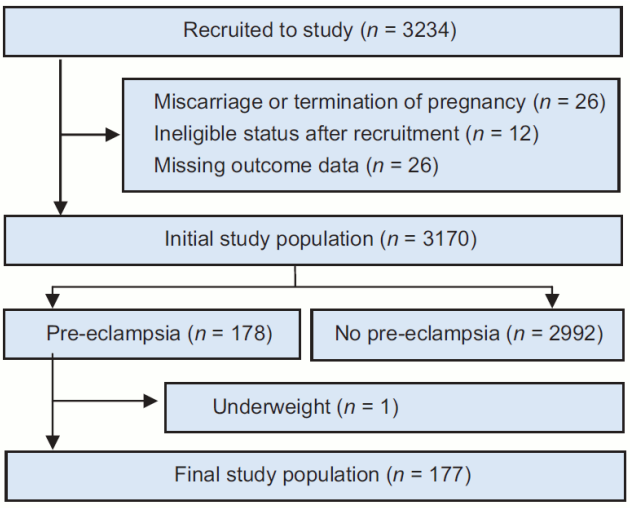


Figure 8.1. Flow of study participants

Table 8.1. Among women with pre-eclampsia, rates of term and preterm pre-eclampsia, abnormal uterine Doppler indices, multi-system complications, SGA and LGA infants according to body mass index categories

	Pre-eclampsia		
	Normal weight (*n* = 66)	Overweight (*n* = 52)	Obese (*n* = 59)
Term pre-eclampsia (delivered ≥37 weeks)	48 (73)	39 (75)	44 (75)
Preterm pre-eclampsia (delivered <37 weeks)	18 (27)	13 (25)	15 (25)
Uterine artery Doppler indices*			
Abnormal uterine artery RI	14 (22)	9 (18)	11 (19)
Bilateral notch	12 (19)	11 (22)	10 (17)
Multi-system complications	34 (52)	19 (37)	24 (41)
SGA (<10th customised centile)	16 (24)	11 (21)	16 (27)
LGA (>90th customised centile)	4 (6)	6 (12)	8 (14)

Results are expressed as *n* (%). All comparisons between normal weight, overweight and obese were non-significant (*P* > 0.10).
***Performed at 19–21 weeks; missing data in Normal *n* = 3, missing data in Overweight *n* = 2.**

Results

Of 3234 women recruited to the SCOPE study in Auckland and Adelaide, 38 (1.2%) women were excluded after recruitment because of miscarriage, termination of pregnancy or ineligible status discovered after recruitment. Follow-up was complete in 3170 (99.2%) of eligible participants (Figure 8.1) of whom 178 (5.6%) developed pre-eclampsia. The overall rate of pre-eclampsia increased with increasing BMI (1.8% in underweight women, *n* = 1 of 55, not shown in figure; 4.0% in normal weight women, *n* = 66 of 1669, 5.7% in overweight women *n* = 52 of 899, and 10.7% in obese women, *n* = 59 of 547, Figure 8.2). After exclusion of the woman who was underweight, the final population with pre-eclampsia in this study was 177.

Among women with pre-eclampsia, pregnancy characteristics relating to pre-eclampsia phenotype according to BMI groups, are shown in Table 8.1. There were no differences in the rates of term / preterm pre-eclampsia, abnormal uterine artery indices, pre-eclampsia with multi-system complications, SGA or LGA between overweight or obese women with pre-eclampsia and women with pre-eclampsia and a normal BMI in early pregnancy (all *P* values >0.10).

Maternal and infant characteristics of women with term and preterm pre-eclampsia are shown in Table 8.2. Compared with the preterm pre-eclampsia group, women with term pre-eclampsia were younger, had lower blood pressure in early pregnancy, and were less likely to have multi-system complications, abnormal uterine artery Doppler indices or an SGA infant. After adjusting for maternal age, primigravidity, ethnicity, mean arterial blood pressure at 14–16 weeks of gestation and SGA, the BMI group was not associated with term pre-eclampsia (*P* = 0.56). There was no interaction between BMI and SGA (*P*= 0.25).

Table 8.2. Characteristics of term (≥ 37 weeks of gestation) and preterm pre-eclampsia

	Pre-eclampsia		
	Term (*n* = 131)	Preterm (*n* = 46)	*P* value
Maternal characteristics at 14–16 weeks			
Body mass index*			
Normal (%)	48 (37)	18 (39)	0.95
Overweight (%)	39 (30)	13 (28)	
Obese (%)	44 (33)	15 (33)	
Maternal age (years)	26 (5.5)	28 (6.0)	0.05
White ethnicity (%)	111 (85)	40 (87)	0.71
Primigravida (%)	103 (79)	31 (67)	0.13
Family history of pre-eclampsia (%)	24 (18)	10 (22)	0.61
Systolic blood pressure (mmHg)	113 (10.5)	117 (12.7)	0.06
Diastolic blood pressure (mmHg)	68 (7.7)	72 (9.8)	0.02
Uterine artery Doppler indices at 19–21 weeks**			
Mean uterine artery RI	0.58 (0.10)	0.66 (0.12)	<0.01
Abnormal uterine artery RI (%)	13 (10)	21 (47)	<0.01
Bilateral notch (%)	16 (12)	17 (37)	<0.01
Maternal characteristics at end of pregnancy			
Gestation at diagnosis of pre-eclampsia (weeks)***	38.2 (2.1)	33.1 (2.7)	
Maximum systolic blood pressure (mmHg)	160 (15)	176 (23)	<0.01
Maximum diastolic blood pressure (mmHg)	101 (9)	113 (9)	<0.01
Proteinuria (%)	112 (86)	42 (91)	0.31
Multi-system complications (%)	49 (37)	28 (61)	<0.01
Pregnancy outcomes			
Gestation at delivery (weeks)	39.1 (1.3)	34.4 (2.2)	
Birthweight (g)	3370 (501)	2062 (644)	<0.01
SGA (<10th customised centile) (%)	17 (13)	26 (57)	<0.01

Results expressed as mean (SD) or *n* (%) as appropriate. *P* values are comparisons between groups using chi-squared or Student's *t* test as appropriate.
***Body mass index according to ethnicity-specific categories.**
****Missing data in Term *n* = 4, Preterm *n* = 1.**
*****Missing data in Term *n* = 4.**

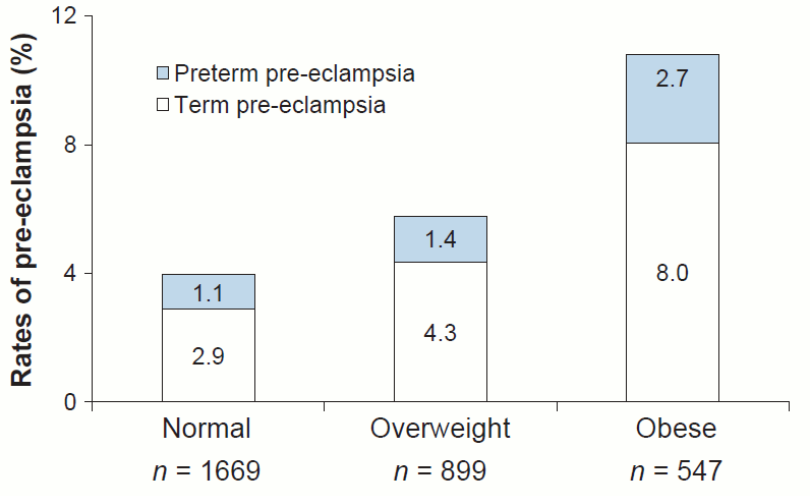


Figure 8.2. The rate of term (≥37 weeks of gestation) and preterm pre-eclampsia by body mass index classification among the cohort (*n* = 3170).

Kaplan-Meier survival analyses of gestational age at onset of pre-eclampsia by BMI category showed similar profiles with no difference between groups (*P*=0.12), Figure 8.3.

Analyses were also performed using standard WHO BMI categories for all women, and no changes in statistical significance were observed.

As this is a secondary analysis of data from the SCOPE study, we performed a sample size calculation to determine if there was adequate power to detect a clinically important difference between groups. Among nulliparous women with pre-eclampsia, if the true proportion of term pre-eclampsia was 70% in women of normal weight (B. Sibai et al., 2005; Xiong, Demianczuk, Saunders, Wang, & Fraser, 2002) and 90% in women who were overweight or obese, then at an α value of 0.05 we had power of approximately 80% to detect this difference with the number of women observed.

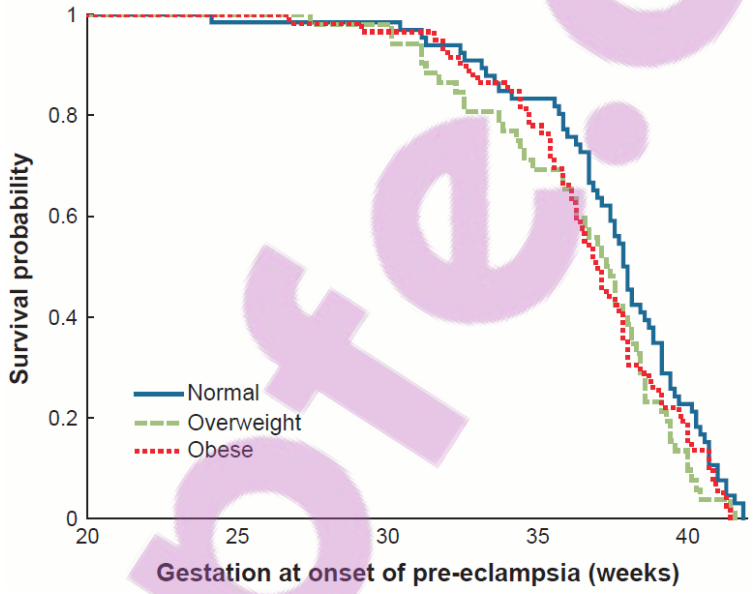


Figure 8.3. Kaplan–Meier survival of gestation at onset of pre-eclampsia according to ethnic-specific body mass index category.

Discussion

Although it is well established that obese women are at increased risk of pre-eclampsia (Mbah et al., 2010; O'Brien et al., 2003; Odegard et al., 2000; B. Sibai et al., 2005; B. M. Sibai et al., 1997), we report that overweight and obese women are at increased risk of both preterm and term preeclampsia. This is the first prospective study to provide detailed information about the clinical phenotype of pre-eclampsia in women who were overweight and obese in early pregnancy. Contrary to our hypothesis, the phenotype of pre-eclampsia in nulliparous women did not differ according to maternal BMI categories. Overweight and obese women with pre-eclampsia were not more likely to have term pre-eclampsia than women of normal weight with pre-eclampsia and had similar rates of abnormal uterine artery Doppler indices and SGA infants.

With rising rates of obesity in the general population, the incidence of pre-eclampsia has increased (LaCoursiere, Bloebaum, Duncan, & Varner, 2005). Obesity and pre-eclampsia have a number of biochemical and physiological changes in common, including increased oxidative stress, inflammation, hyperlipidemia, endothelial dysfunction and vasoconstriction (Callaway, O'Callaghan, & McIntyre, 2009; Walsh, 2007). This has given credence to the concept of an exaggerated maternal response occurring in obese women that typically manifests as late onset or term pre-eclampsia. However, we demonstrate that the rates of both preterm and term pre-eclampsia increase proportionally with higher maternal BMI. This suggests that the predisposition to pre-eclampsia conferred with obesity contributes both to impaired placentation associated with preterm pre-eclampsia and the exaggerated maternal response seen in term pre-eclampsia.

Consistent with our findings, a case-control study from Norway reported an increase in both early and late pre-eclampsia in women weighing more than 70kg compared to those whose weight was less than 70kg at pregnancy booking (Odegard et al., 2000). A large retrospective study found increasing rates of pre-eclampsia with increased BMI, but found a stronger odds ratio association between obesity and late-onset (≥34 weeks of gestation) pre-eclampsia compared with early-onset (<34 weeks of gestation) pre-eclampsia (Mbah et al., 2010). Despite this association, the absolute percentages of women with early-onset and late-onset pre-eclampsia in the normal BMI group and each of the obesity categories were very similar (Mbah et al., 2010). Of interest, Mbah et al. (Mbah et al., 2010) also reported that mothers with early-onset pre-eclampsia had a higher self reported pre-pregnancy BMI (27.5) than the mean BMI (24.6) in women with late-onset pre-eclampsia. The use of self-reported maternal pre-pregnancy weight was acknowledged as a limitation in this study as overweight and obese pregnant women are more likely to under-report weight and over-report height (Craig & Adams, 2009; Mbah et al., 2010).

A strength of our study is the longitudinal tracking throughout pregnancy which enabled us to accurately measure early pregnancy height, weight and blood pressure and, at 19–21 weeks of gestation, to perform uterine artery Doppler studies as a surrogate for utero-placental perfusion. The BMI was calculated using weight and height measured by a research midwife at 14–16 weeks of gestation rather than rely on recall of pre-pregnancy weight due to the bias of underestimation of weight in pregnancy (Craig & Adams, 2009). There are no data to date on whether first trimester weight gain differs between women who develop term compared to pre-term pre-eclampsia, but is unlikely to have substantially changed the BMI classification of participants. Additionally, our cohort included women of different ethnicities, so we used ethnicity-specific BMI criteria to adjust for differences in the ratio of body fat to lean body mass

and provide more accurate classification of obesity than the standard WHO criteria. Of note, results were unchanged when all women were classified using standard WHO criteria.
A potential limitation of this study is that smaller differences between groups may not be detected secondary to our study size. It is unlikely that the minimal missing data on uterine artery Doppler RI (n = 5) would have influenced our findings.

Conclusion

Contrary to our hypothesis, among nulliparous women with pre-eclampsia we did not find a higher occurrence of term pre-eclampsia in overweight and obese women when compared with women with pre-eclampsia and a normal BMI. Further, overweight and obese women were not less likely to have abnormal uterine artery Doppler studies or SGA infants than women with a normal BMI. These findings aid our understanding of the phenotypes of pre-eclampsia occurring in overweight and obese mothers and suggest that the increased rate of pre-eclampsia with an elevated BMI is not solely due to an exaggerated maternal response to pregnancy late in gestation. Overweight and obese women therefore require vigilant surveillance for the development of preterm as well as term pre-eclampsia.

Disclosure of Interests

RN has consultancy relationships with Pronota and Alere and declares patent PCT number WO/2009/108073.

Funding

New Zealand SCOPE Study: New Enterprise Research Fund, Foundation for Research Science and Technology; Health Research Council; Evelyn Bond Fund, Auckland District Health Board Charitable Trust.
Australian SCOPE Study: Premier's Science and Research Fund, South Australian Government
NA was supported by the Douglas Goodfellow Medical Research Fellowship from the Auckland Medical Research Foundation, Auckland, New Zealand.

Acknowledgements

We would like to thank the pregnant women who participated in the SCOPE study, Associate Professor Claire Roberts for her contributions in establishing the SCOPE study in Adelaide, Denise Healy for coordinating the Australian SCOPE study and the SCOPE research midwives.

References

Bodnar, L. M., Catov, J. M., Klebanoff, M. A., Ness, R. B., & Roberts, J. M. (2007). Prepregnancy body mass index and the occurrence of severe hypertensive disorders of pregnancy. *Epidemiology, 18*(2), 234-239.

Callaway, L. K., O'Callaghan, M., & McIntyre, H. D. (2009). Obesity and the hypertensive disorders of pregnancy. *Hypertension in Pregnancy, 28*(4), 473-493.

Craig, B. M., & Adams, A. K. (2009). Accuracy of body mass index categories based on self-reported height and weight among women in the United States. *Maternal & Child Health Journal, 13*(4), 489-496. doi:10.1007/s10995-008-0384-7

Groom, K. M., North, R. A., Poppe, K. K., Sadler, L., & McCowan, L. M. E. (2007). The association between customised small for gestational age infants and pre-eclampsia or gestational hypertension varies with gestation at delivery. *BJOG: An International Journal of Obstetrics & Gynaecology, 114*(4), 478-484.

Groom, K. M., North, R. A., Stone, P. R., Chan, E. H. Y., Taylor, R. S., Dekker, G. A., . . . on behalf of the SCOPE consortium. (2009). Patterns of change in uterine artery Doppler studies between 20 and 24 weeks of gestation and pregnancy outcomes. *Obstetrics & Gynecology, 113*(2 Pt 1), 332-338.

Huppertz, B. (2008). Placental origins of preeclampsia: challenging the current hypothesis. *Hypertension, 51*(4), 970-975.

LaCoursiere, D. Y., Bloebaum, L., Duncan, J. D., & Varner, M. W. (2005). Population-based trends and correlates of maternal overweight and obesity, Utah 1991-2001. *American Journal of Obstetrics & Gynecology, 192*(3), 832-839.

Mbah, A. K., Kornosky, J. L., Kristensen, S., August, E. M., Alio, A. P., Marty, P. J., . . . Salihu, H. M. (2010). Super-obesity and risk for early and late pre-eclampsia. *BJOG: An International Journal of Obstetrics & Gynaecology, 117*(8), 997-1004.

McCowan, L. M. E., North, R., & Taylor, R. (2007). ACTRN12607000551493. *Australian New Zealand Clinical Trials Registry*. from www.anzctr.org.au/trialSearch.aspx

McCowan, L. M. E., Stewart, A. W., Francis, A., & Gardosi, J. (2004). A customised birthweight centile calculator developed for a New Zealand population. *Australian & New Zealand Journal of Obstetrics & Gynaecology, 44*(5), 428-431.

North, R. A., McCowan, L. M., Dekker, G. A., Poston, L., Chan, E. H., Stewart, A. W., . . . Kenny, L. C. (2011). Clinical risk prediction for pre-eclampsia in nulliparous women: development of model in international prospective cohort. *BMJ, 342*, d1875.

O'Brien, T. E., Ray, J. G., & Chan, W. S. (2003). Maternal body mass index and the risk of preeclampsia: a systematic overview. *Epidemiology, 14*(3), 368-374.

Odegard, R. A., Vatten, L. J., Nilsen, S. T., Salvesen, K. A., & Austgulen, R. (2000). Risk factors and clinical manifestations of pre-eclampsia. *BJOG, 107*(11), 1410-1416.

Sibai, B., Dekker, G., & Kupferminc, M. (2005). Pre-eclampsia. *Lancet, 365*(9461), 785-799.

Sibai, B. M., Ewell, M., Levine, R. J., Klebanoff, M. A., Esterlitz, J., Catalano, P. M., . . . Joffe, G. (1997). Risk factors associated with preeclampsia in healthy nulliparous women. The Calcium for Preeclampsia Prevention (CPEP) Study Group. *American Journal of Obstetrics & Gynecology, 177*(5), 1003-1010.

Stone, J. L., Lockwood, C. J., Berkowitz, G. S., Alvarez, M., Lapinski, R., & Berkowitz, R. L. (1994). Risk factors for severe preeclampsia. *Obstetrics & Gynecology, 83*(3), 357-361.

Vatten, L. J., & Skjaerven, R. (2004). Is pre-eclampsia more than one disease? *BJOG: An International Journal of Obstetrics & Gynaecology, 111*(4), 298-302.

von Dadelszen, P., Magee, L. A., & Roberts, J. M. (2003). Subclassification of preeclampsia. *Hypertension in Pregnancy, 22*(2), 143-148.

Walsh, S. W. (2007). Obesity: a risk factor for preeclampsia. *Trends in Endocrinology & Metabolism, 18*(10), 365-370.

WHO/IASO/IOTF. (2000). The Asia-Pacific perspective: Redefining Obesity and its Treatment. Melbourne.

World Health Organization. (2000). *Obesity: Preventing and Managing the Global Epidemic: report of a WHO Consultation* (WHO Technical Report Series 894). Geneva, Switzerland: World Health Organisation.

Xiong, X., Demianczuk, N. N., Saunders, L. D., Wang, F. L., & Fraser, W. D. (2002). Impact of preeclampsia and gestational hypertension on birth weight by gestational age. *American Journal of Epidemiology, 155*(3), 203-209.

Chapter 9. | Ethnicity, body mass index and pre-eclampsia

9.1. Preamble

The manuscript reproduced below was published in The Australian and New Zealand Journal of Obstetrics and Gynaecology (ANZJOG) on 1st October 2012.

Permission

Reproduced from: Anderson N H, Sadler L C, Stewart A W, Fyfe E M, McCowan L M E. *Ethnicity, body mass index and risk of pre-eclampsia in a multiethnic New Zealand population.* Australian & New Zealand Journal of Obstetrics & Gynaecology, 2012; 52(6)552-558.

Received 3 May 2012; accepted 13 July 2012.

9.2. Manuscript: Ethnicity, body mass index and pre-eclampsia

Abstract

Background: Pre-eclampsia rates are reported to vary by ethnicity however few studies include body mass index (BMI). Increasing BMI has a dose-dependent relationship with pre-eclampsia, and rates of overweight and obesity as well as ratios of body-fat to muscle mass differ between ethnicities. We hypothesised that after adjusting for confounders, including ethnic-specific BMI, ethnicity would not be an independent risk factor for pre-eclampsia.

Aim: To assess independent pre-eclampsia risk factors in a multi-ethnic New Zealand population.

Methods: We performed a retrospective cohort analysis of prospectively recorded maternity data from 2006 to 2009 at National Women's Health, Auckland, New Zealand. After exclusion of infants with congenital anomalies and missing data, our final study population was 26 254 singleton pregnancies. Multivariable logistic regression analysis adjusted for ethnicity, BMI, maternal age, parity, smoking, social deprivation, diabetes, chronic hypertension and relevant pre-existing medical conditions was performed.

Results: Independent associations with pre-eclampsia were observed in Chinese (adjusted odds Ratio (aOR) 0.56, [95% CI 0.41–0.76]) and Māori (aOR 1.51, [1.16–1.96]) compared with European women. Other independent risk factors for pre-eclampsia were overweight and obesity, nulliparity, type 1 diabetes, chronic hypertension and pre-existing medical conditions.

Conclusions: Contrary to our hypothesis, we report an independent reduced risk of pre-eclampsia in Chinese and increased risk of pre-eclampsia in Māori women. Prospective studies are required to further explore these relationships. Other independent risk factors are

consistent with international literature. Our findings may assist clinicians to stratify risk of pre-eclampsia in clinical practice.

Introduction

Pre-eclampsia, which affects between 2 and 7% of all pregnancies, is an important cause of maternal and perinatal morbidity and mortality globally (B. Sibai, Dekker, & Kupferminc, 2005). Rates of pre-eclampsia have been reported to vary by ethnicity with African American women consistently showing an increased risk (Caughey, Stotland, Washington, & Escobar, 2005; Tanaka et al., 2007) and Chinese women a reduced risk (Caughey et al., 2005; Leung et al., 2008; Rao, Daniels, El-Sayed, Moshesh, & Caughey, 2006) compared to European. Previous studies that have investigated the relationship between ethnicity and risk of pre-eclampsia have adjusted for a limited number of confounders, but few have adjusted for maternal body mass index (BMI). Increasing maternal BMI has an independent, dose dependent relationship with increased risk of pre-eclampsia (Bodnar, Ness, Markovic, & Roberts, 2005), but rates of overweight and obesity differ between ethnicities (Ministry of Health, 2008), confounding the association between ethnicity and pre-eclampsia. Studies that include both ethnicity and BMI are either cohorts of nulliparous women only (Knuist, Bonsel, Zondervan, & Treffers, 1998; B. M. Sibai et al., 1997), or North American ethnic groups that are not applicable to a general New Zealand obstetric population. In New Zealand, a single study reported no excess pre-eclampsia risk in Pacific or Māori women after adjustment for obesity alone (Stone et al., 1995), and a recent prospective study in nulliparous women showed no univariable differences in rates of pre-eclampsia between ethnicities (North et al., 2011), but was underpowered to investigate ethnicity with small numbers of non-European women.

In adults with the same BMI, percentage of body-fat compared to lean muscle mass varies by ethnic group. Specifically Asian and Indian adults have a higher percentage of body fat (Deurenberg, Deurenberg-Yap, & Guricci, 2002; World Health Organization expert consultation, 2004), and Polynesian adults a lower percentage of body fat (i.e. are leaner) compared with European adults of the same BMI (Swinburn, Ley, Carmichael, & Plank, 1999). Consistent with this finding, non-pregnant Asian and Indian adults have been found to have an increased risk of diabetes, hypertension and dyslipidaemia at lower BMI levels than European adults (World Health Organization expert consultation, 2004). To address these variations in adiposity and adiposity-related risk between ethnic groups, ethnic-specific definitions of overweight and obesity have been developed whereby Asian BMI thresholds for overweight and obesity are lowered and Māori and Pacific BMI thresholds are raised compared with standard World Health Organization (WHO) definitions (Swinburn et al., 1999; World Health Organization expert consultation, 2004).

A single study has investigated the appropriateness of using lowered BMI criteria for overweight and obesity in a cohort of pregnant Chinese women and confirmed that the risk of obstetric complications was increased at BMI levels considered normal by WHO criteria (Leung et al., 2008).

In our multiethnic New Zealand cohort we aimed to;

1 identify clinical risk factors independently associated with pre-eclampsia, and

2 assess the independent association between ethnicity and pre-eclampsia. We hypothesised that after adjusting for confounding factors, including ethnic-specific BMI, ethnicity would not be an independent risk factor for pre-eclampsia.

Materials and Methods

National Women's Health (NWH) is a tertiary referral service at Auckland City Hospital, Auckland, New Zealand with a diverse ethnic population and approximately 7500 maternities per year. The NWH clinical database of births from 2006 to 2009 was used for this study. This database consists of de-identified, prospectively collected maternity data for all births occurring at ≥20 weeks of gestation, which includes demographic data, antenatal complications, and detailed delivery and newborn data. Data are routinely checked for completeness, out of range values and inconsistency (National Women's Health, 2012). Ethical approval for this study was gained from the Northern X Regional Ethics Committee (NTX/09/179/EXP).

Included in the study were women with singleton pregnancies delivered at NWH from January 2006 to December 2009, *n* = 29 573. After exclusion of infants with major congenital anomalies (*n* = 415) and women with missing data for maternal height and/or weight (*n* = 2901) or infant birthweight (*n* = 3), the final study population comprised 26 254 women, Figure 9.1.

Pre-eclampsia was defined as per the International Society for the Study of Hypertension in Pregnancy recommendations as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90mmHg on at least two occasions 4 h apart after 20 weeks of gestation, with either proteinuria (24 hour urinary protein ≥300 mg or spot urine protein/creatinine ratio ≥30 mg/mmol creatinine or urine dipstick protein ≥2+) or any multi-system complication of pre-eclampsia (Brown, Lindheimer, de Swiet, Van Assche, & Moutquin, 2001). Women were also considered to have pre-eclampsia if there was evidence of HELLP syndrome (hemolysis, elevated liver enzymes and a low platelet count) without hypertension (Lowe et al., 2009), or if one or more of the systemic features of pre-eclampsia developed after 20 weeks' gestation on a background of chronic hypertension (defined as hypertension before 20 weeks gestation, or a medical history of essential hypertension).

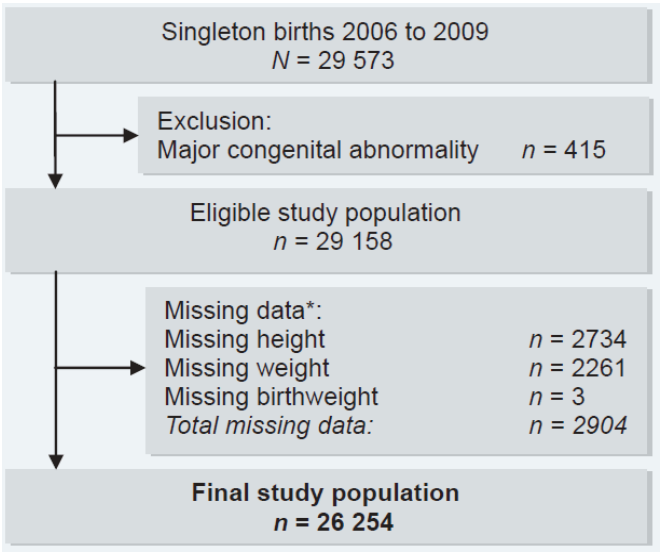


Figure 9.1. Flow chart of participants
***Data may be missing for >1 variable, so numbers do not total**

Variables considered *a priori* risk or protective factors for pre-eclampsia were ethnicity, ethnic-specific BMI, maternal age, parity, cigarette smoking status, socioeconomic status, diabetes, chronic hypertension and other pre-existing medical conditions.

Ethnicity was self-determined and prioritised as per New Zealand Ministry of Health guidelines (Ministry of Health, 2004). Other Asian ethnicity included women from South-East Asia and the Indian subcontinent (excluding India).

Maternal height and weight were recorded at the first antenatal booking visit and measured to the nearest centimetre and kilogram, respectively. Women were classified into normal, overweight and obese groups according to ethnic-specific criteria (World Health Organization expert consultation, 2004) with lower BMI criteria for overweight and obesity in Asian/Indian women (normal 18.5–22.9 kg/m^2, overweight 23–27.4 kg/m^2 and obese ≥ 27.5 kg/m^2) and higher BMI criteria for overweight and obesity in Pacific and Māori women (normal 18.5–25.9 kg/m^2, overweight 26–31.9 kg/m^2 and obese ≥ 32 kg/m^2). For European women and women of all other ethnicities, standard WHO criteria were used (normal 18.5–24.9 kg/m^2, overweight 25–29.9 kg/ m^2 and obese ≥ 30 kg/ m^2) (World Health Organization expert consultation, 2004).

Parity was defined as the number of times a woman had given birth to liveborn or stillborn infant(s) of any birthweight from 20 weeks of gestation, or if gestation was unknown, where the infant weighed ≥400g (Bai, Wong, Bauman, & Mohsin, 2002). Cigarette smoking status was recorded both at booking and at delivery. If a woman was smoking at either time point they were defined as a smoker for the purposes of this study. Socioeconomic status was estimated using a centile score (range 1–10) based on residential area deprivation data from the 2006 New Zealand census (NZDep2006) (Salmond, Crampton, & Atkinson, 2007). Centile scores were

condensed into quintiles (range 1–5) with no change in significance of analyses, where quintile 1 represented the least deprived residential areas and quintile 5 the most deprived areas.
Diabetes was classified into pre-pregnancy (type 1 or type 2 diabetes mellitus), gestational diabetes mellitus (GDM) or unknown diabetes status. GDM was diagnosed using the Australasian Diabetes in Pregnancy Society guidelines (Hoffman, Nolan, Wilson, Oats, & Simmons, 1998). Pre-existing medical conditions included anti-phospholipid syndrome, renal disease and systemic lupus erythematosus (Duckitt & Harrington, 2005).

Statistical Methods

Univariable analysis of categorical data was performed using the chi square test, and continuous variables were compared using Student's *t*-test assuming equality of variance. A *P*-value < 0.05 was considered significant. Crude and adjusted odds ratios (OR and aOR) with 95% CI were calculated using simple and multivariable logistic regression, with all *a priori* variables included in the multivariable logistic regression model. Referent groups for pathological variables (smoking status, diabetes, chronic hypertension and pre-existing medical conditions) were those women without the respective pathology, and all other referent groups are indicated in Table 9.1.
All statistical tests were performed using SAS© version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

Preeclampsia occurred in 3.3% (*n* = 857) of our study population. Characteristics of the study population by pre-eclampsia status are presented in Table 9.1, and late pregnancy outcomes by pre-eclampsia status are presented in Table 9.2. Of note, over a quarter of infants of pre-eclamptic women (*n* = 221, 25.8%) were delivered pre-term (<37 weeks of gestation), and the rate of SGA in infants of pre-eclamptic women was more than doubled compared with women without pre-eclampsia (*n* = 244, 28.5% versus *n* = 2743, 10.8%). The rate of pre-eclampsia in women excluded for missing data was higher than in the study population (4.5%, *n* = 130/2904 compared with 3.3%, *P* <0.01). These excluded women are at greater risk of pre-eclampsia than the general population as they include a high proportion of women transferred for tertiary care or unbooked (*n* = 676, 23%).

Table 9.1. Characteristics of study population by pre-eclampsia status, with crude and adjusted odds ratios (OR, [95% CI]) for pre-eclampsia

	Pre-eclampsia		No pre-eclampsia		Crude		Adjusted		
	n = 857	3.3%	*n* = 25 397	96.7%	OR	95% CI	OR	95% CI	*P*-value*
Maternal ethnicity									
European	409	3.1	12 670	96.9	Ref		Ref		<0.01
Māori	90	4.7	1823	95.3	1.53	1.21–1.93	1.51	1.16–1.96	
Pacific	164	4.5	3521	95.5	1.44	1.20–1.74	1.25	0.99–1.57	
Chinese	48	1.5	3100	98.5	0.48	0.36–0.65	0.56	0.41–0.76	
Indian	78	4.2	1791	95.8	1.35	1.05–1.73	1.20	0.92–1.56	
Other Asian	52	3.1	1616	96.9	1.00	0.74–1.34	1.02	0.76–1.38	
Other ethnicity	16	1.8	876	98.2	0.57	0.34–0.94	0.64	0.38–1.06	
BMI (ethnic specific)									
Underweight	11	1.2	940	98.8	0.52	0.28–0.95	0.58	0.31–1.06	<0.01
Normal	297	2.2	13 204	97.8	Ref		Ref		
Overweight	275	3.9	6769	96.1	1.81	1.53–2.13	1.77	1.49–2.10	
Obese	274	5.8	4484	94.2	2.72	2.30–3.21	2.56	2.11–3.09	
Maternal age (years)									
<20	38	4.8	749	95.2	1.42	1.00–2.00	1.08	0.75–1.55	0.19
20–29	290	3.5	8092	96.5	Ref		Ref		
30–34	274	3.1	8653	96.9	0.88	0.75–1.05	1.04	0.86–1.24	
35–39	189	2.9	6431	97.1	0.82	0.68–0.99	1.00	0.82–1.23	
≥40	66	4.3	1472	95.7	1.25	0.95–1.64	1.42	1.05–1.91	
Parity									
0	550	4.3	12 310	95.7	2.08	1.75–2.46	2.40	2.01–2.86	<0.01
1	182	2.1	8461	97.9	Ref		Ref		
2	63	2.2	2882	97.8	1.04	0.78–1.39	0.88	0.65–1.18	
≥3	62	3.3	1804	96.7	1.60	1.19–2.14	0.98	0.71–1.34	
Smoking	86	3.5	2391	96.5	1.07	0.86–1.35	0.81	0.64–1.04	0.10
Deprivation quintile (NZDep2006)†									
1	131	2.8	4575	97.2	Ref		Ref		0.87
2	164	3.2	4996	96.8	1.15	0.91–1.45	1.06	0.84–1.34	
3	170	3.0	5463	97.0	1.09	0.86–1.37	0.97	0.77–1.24	
4	209	3.7	5399	96.3	1.35	1.08–1.69	1.06	0.84–1.34	
5	183	3.6	4964	96.4	1.29	1.03–1.62	0.98	0.76–1.25	
Diabetes									
Gestational	59	4.1	1391	95.9	1.37	1.04–1.81	1.00	0.75–1.33	<0.01
Type 1	12	9.6	113	90.4	3.44	1.88–6.27	2.84	1.52–5.33	
Type 2	17	7.6	207	92.4	2.66	1.61–4.39	1.38	0.81–2.36	
Unknown	227	3.6	6146	96.4	1.20	1.02–1.40	1.22	1.04–1.43	
No Diabetes	542	2.9	18 080	97.1	Ref		Ref		
Other Medical									
Chronic hypertension	95	14.1	577	85.9	5.36	4.27–6.74	4.65	3.64–5.93	<0.01
Pre-existing medical‡	20	8.4	217	91.6	2.77	1.75–4.41	2.63	1.63–4.23	<0.01

Data presented are *n* % and OR [95% CI] as appropriate. Adjusted ORs are adjusted for all the variables in the table.
***Chi-squared *P*-value for adjusted model.**
†*n* = 13 missing data.
‡Pre-existing medical conditions; renal disease, anti-phospholipid syndrome, systemic lupus erythematosus.

Crude odds for pre-eclampsia were reduced in Chinese women (OR 0.48, [0.36–0.65]) and elevated in Māori (OR 1.53, [95% CI 1.21–1.93]), Pacific (OR 1.44, [1.20–1.74]) and Indian women (OR 1.35, [1.05–1.73]) compared with European, Table 9.1. Similarly, there were significant univariate associations with demographic characteristics (BMI, age, parity and deprivation score). Increasing BMI category had increasing crude odds of pre-eclampsia (Table 9.1) with the distribution of BMI differing greatly by ethnicity, Figure 9.2.

Table 9.2. Late pregnancy outcomes by pre-eclampsia status

	Pre-eclampsia		No pre-eclampsia	
	n = 857	3.3%	*n* = 25 397	96.7%
Gestation at delivery (weeks)	37.2	3.0	38.9	2.1
Preterm birth (<37 weeks)	221	25.8%	1493	5.9%
Birthweight (g)	2948	832	3428	582
Small for gestational age	244	28.5%	2743	10.8%
Perinatal death*	12	14.2	190	7.8

Data presented are *n* % and mean (SD) as appropriate. All *P*-values < 0.01.
***Stillbirth and neonatal death (to one month after birth) rate per 1000 total births.**

Ethnic-specific and WHO BMI distributions by ethnicity are also shown in Figure 9.2. Median BMI (inter-quartile range) ranged from 21.3kg/m^2 (19.6–23.4) in Chinese women to 32.0 kg/m^2 (27.4–36.9) in Pacific women. Rates of pre-eclampsia also increased with increasing BMI category in all ethnicities (data not shown). Parity had a 'U' shaped univariable association with higher crude odds of pre-eclampsia in nulliparous women and women with parity ≥3. High deprivation quintile areas had higher crude odds of pre-eclampsia than low deprivation quintile areas. Rates of cigarette smoking in our cohort were low (*n* = 2477, 9.4%) and varied substantially by ethnicity (data not shown); however, there were no differences in smoking rates between women with and without pre-eclampsia. Diabetes, chronic hypertension and pre-existing medical conditions were all associated with pre-eclampsia in univariable analysis, Table 9.1.

After multivariable analysis, ethnicity remained independently associated with pre-eclampsia with a reduced odds in Chinese (aOR 0.56, [0.41–0.76]) and an increased odds in Māori women (aOR 1.51, [1.16–1.96]), Table 9.1. Other independent risk factors for pre-eclampsia were overweight and obesity, nulliparity, type 1 diabetes, unknown diabetes status, chronic hypertension and pre-existing medical conditions.

For completeness, multivariable analysis was also performed using standard WHO BMI criteria and no change in overall statistical significance was observed. There was an increase in aOR point estimate for Indian ethnicity compared to European that became statistically significant (aOR 1.41, [1.08–1.83]), while all other ethnicity aOR point estimates had small differences without change in statistical significance.

Discussion

In our multiethnic study, we report that contrary to our hypothesis, ethnicity was independently associated with risk of pre-eclampsia. In particular, compared with European, women of Chinese ethnicity had a nearly 50% reduction in risk and Māori women a 50% increased risk of pre-eclampsia after controlling for confounding factors, including ethnic-specific BMI. Consistent with prior knowledge, other independent clinical risk factors for pre-eclampsia in our cohort were maternal overweight and obesity, nulliparity, diabetes, chronic hypertension and previous medical conditions (Duckitt & Harrington, 2005; B. Sibai et al., 2005).

Our finding of a reduced risk of pre-eclampsia among Chinese women is consistent with the few previous publications which report lower rates of pre-eclampsia in Chinese than in European populations (Caughey et al., 2005; Leung et al., 2008; Rao et al., 2006). In our study, this effect was independent of other commonly described risk factors for pre-eclampsia, including BMI. The mechanisms underlying this finding are unknown and may be related to lifestyle or genetic factors or combinations of these. For example a high fruit intake has been reported as associated with reduced odds for pre-eclampsia in healthy nulliparous women (North et al., 2011), and differences in diet have been reported between Chinese and European adults living in the same country (Tam et al., 2011). Lifestyle factors such as these may contribute to this finding of reduced risk in Chinese women. Further research to investigate the potential protective mechanisms in Chinese women may contribute to improved understanding of the pathophysiology of pre-eclampsia.

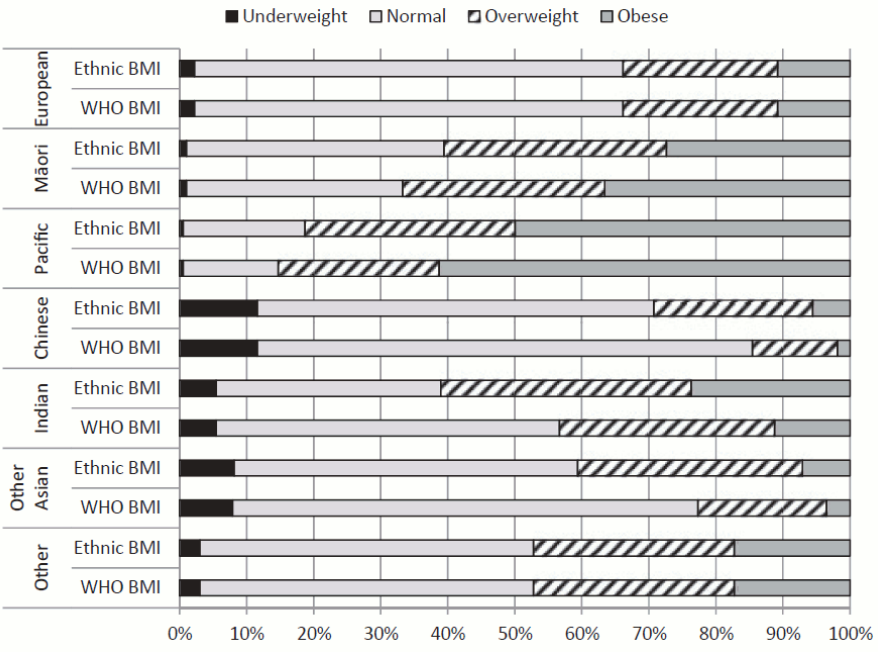


Figure 9.2. Comparison of ethnic-specific (ethnic) and World Health Organization BMI distributions by ethnicity.

Our data reporting an increased risk of pre-eclampsia among Māori women are novel and appear to be independent of confounding factors which are more prevalent in Māori adults such as obesity and chronic hypertension (Ministry of Health, 2008). The mechanism for this elevated risk of pre-eclampsia in Māori women is unknown, but we speculate that it may be related to metabolic factors. For example, non-pregnant Māori adults have been reported to have decreased adiponectin levels compared with European (Shand, Elder, Scott, Poa, & Frampton, 2007). Adiponectin has insulin-sensitising and anti-atherosclerotic properties and reduced levels have been associated with an increased risk of type 2 diabetes (Ahima, 2006). Low adiponectin levels in the first trimester have also been associated with an increased risk of later pre-eclampsia (D'Anna et al., 2006).

Compared with European women, Indian women had a non-significant increase in risk of pre-eclampsia which became statistically significant when WHO BMI criteria were used in the multivariable analysis. WHO BMI criteria may misclassify adiposity in Indian women, leading to an over-estimate of risk of pre-eclampsia (World Health Organization expert consultation, 2004). Alternatively an elevated risk of pre-eclampsia in Indian women could potentially be explained by background metabolic differences, as Indian adults (similar to Māori) have higher rates of dyslipidaemia, hypertension and cardiovascular disease than European (Ministry of Health, 2008; Qiao, Gao, Zhang, Nyamdorj, & Tuomilehto, 2007).

We believe the use of ethnic-specific BMI criteria to classify overweight and obesity in this study allows for better categorisation of adiposity in non-European ethnicities. Comparisons between ethnicities using ethnic specific BMI criteria as opposed to WHO BMI criteria classify women with a similar body fat to lean-body-mass ratio in the same group (Swinburn et al., 1999; World Health Organization expert consultation, 2004). This may be of particular relevance to studies of pre-eclampsia, which has similarities in pathophysiology to obesity including features such as oxidative stress, inflammation, hyperlipidemia, endothelial dysfunction and vasoconstriction (Callaway, O'Callaghan, & McIntyre, 2009). Very large studies would be required to directly compare ethnic-specific BMI and WHO BMI in relation to risk of pre-eclampsia.

We found a trend towards a reduced risk of pre-eclampsia in women who smoked; however, this was not statistically significant which may be due to the overall low rate of cigarette smoking in our cohort (<10%). Smoking has usually been reported to be associated with a reduced risk of pre-eclampsia (Conde-Agudelo, Althabe, Belizan, & Kafury-Goeta, 1999).

An increased risk of pre-eclampsia observed in women with GDM and type 2 diabetes did not persist after adjustment for confounding factors including BMI. It is well documented that GDM, type 2 diabetes and obesity are highly correlated (Chu et al., 2007), and it is likely the high prevalence of overweight and obesity among women with GDM or type 2 diabetes explains the initial univariable association. Additionally, an increased risk of pre-eclampsia was seen in

women who had unknown diabetes status (*n* = 6373, 24%; aOR 1.22, [1.04-1.43]). In the NWH clinical database, women with unknown diabetes status are a heterogenous group who were either not screened (including women with poor antenatal attendance or late booking) or were screen negative and this information was not recorded. Women who have poor antenatal attendance or book late in gestation may have additional risk factors for pre-eclampsia that we were unable to adjust for in our model.

A limitation of this study was that the analysis was performed using a retrospective hospital database, albeit with robust data cleaning. Factors that other investigators have reported to be associated with pre-eclampsia such as high gestational weight gain, past or family history of pre-eclampsia, dietary and lifestyle factors (Duckitt & Harrington, 2005; B. Sibai et al., 2005), were not able to be included as they were not recorded in this database. Additionally, as with any retrospective study, data limitations may result in residual confounding. These effects may possibly account for some of the ethnic associations seen with pre-eclampsia in this study.

Conclusions

We have demonstrated that rates of pre-eclampsia vary significantly in New Zealand ethnic groups with lower rates in Chinese and higher rates in Māori women. As pre-eclampsia is associated with poorer obstetric outcomes, these data provide further evidence of the health disparities that exist, particularly between European and Māori women. The causes of these differences are unclear and prospective studies are required to further explore these relationships. Other independent risk factors for pre-eclampsia in our multiethnic general obstetric cohort are consistent with international literature. Our findings may assist clinicians to stratify risk of pre-eclampsia in clinical practice.

References

Ahima, R. S. (2006). Adipose tissue as an endocrine organ. *Obesity, 14 Suppl 5*, 242S-249S.

Bai, J., Wong, F. W., Bauman, A., & Mohsin, M. (2002). Parity and pregnancy outcomes. *American Journal of Obstetrics & Gynecology, 186*(2), 274-278.

Bodnar, L. M., Ness, R. B., Markovic, N., & Roberts, J. M. (2005). The risk of preeclampsia rises with increasing prepregnancy body mass index. *Annals of Epidemiology, 15*(7), 475-482.

Brown, M. A., Lindheimer, M. D., de Swiet, M., Van Assche, A., & Moutquin, J. M. (2001). The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). *Hypertension in Pregnancy, 20*(1), IX-XIV.

Callaway, L. K., O'Callaghan, M., & McIntyre, H. D. (2009). Obesity and the hypertensive disorders of pregnancy. *Hypertension in Pregnancy, 28*(4), 473-493.

Caughey, A. B., Stotland, N. E., Washington, A. E., & Escobar, G. J. (2005). Maternal ethnicity, paternal ethnicity, and parental ethnic discordance: predictors of preeclampsia. *Obstetrics & Gynecology, 106*(1), 156-161.

Chu, S. Y., Callaghan, W. M., Kim, S. Y., Schmid, C. H., Lau, J., England, L. J., & Dietz, P. M. (2007). Maternal obesity and risk of gestational diabetes mellitus. *Diabetes Care, 30*(8), 2070-2076.

Conde-Agudelo, A., Althabe, F., Belizan, J. M., & Kafury-Goeta, A. C. (1999). Cigarette smoking during pregnancy and risk of preeclampsia: a systematic review. *American Journal of Obstetrics & Gynecology, 181*(4), 1026-1035.

D'Anna, R., Baviera, G., Corrado, F., Giordano, D., De Vivo, A., Nicocia, G., & Di Benedetto, A. (2006). Adiponectin and insulin resistance in early- and late-onset pre-eclampsia. *BJOG: An International Journal of Obstetrics & Gynaecology, 113*(11), 1264-1269.

Deurenberg, P., Deurenberg-Yap, M., & Guricci, S. (2002). Asians are different from Caucasians and from each other in their body mass index/body fat per cent relationship. *Obesity Reviews, 3*(3), 141-146.

Duckitt, K., & Harrington, D. (2005). Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. *BMJ, 330*(7491), 565.

Hoffman, L., Nolan, C., Wilson, J. D., Oats, J. J., & Simmons, D. (1998). Gestational diabetes mellitus--management guidelines. The Australasian Diabetes in Pregnancy Society (updated Dec 2002). *Medical Journal of Australia, 169*(2), 93-97.

Knuist, M., Bonsel, G. J., Zondervan, H. A., & Treffers, P. E. (1998). Risk factors for preeclampsia in nulliparous women in distinct ethnic groups: a prospective cohort study. *Obstetrics & Gynecology, 92*(2), 174-178.

Leung, T. Y., Leung, T. N., Sahota, D. S., Chan, O. K., Chan, L. W., Fung, T. Y., & Lau, T. K. (2008). Trends in maternal obesity and associated risks of adverse pregnancy outcomes in a population of Chinese women. *BJOG: An International Journal of Obstetrics & Gynaecology, 115*(12), 1529-1537.

Lowe, S. A., Brown, M. A., Dekker, G. A., Gatt, S., McLintock, C. K., McMahon, L. P., . . . Walters, B. (2009). Guidelines for the management of hypertensive disorders of pregnancy 2008. *Australian & New Zealand Journal of Obstetrics & Gynaecology, 49*(3), 242-246.

Ministry of Health. (2004). *Ethnicity Data Protocols for the Health and Disability Sector*. Wellington: Ministry of Health. Retrieved from http://www.nzhis.govt.nz/documentation/ethnicity/index.html

Ministry of Health. (2008). A Portrait of Health. Key Results of the 2006/07 New Zealand Health Survey. Wellington: Ministry of Health.

National Women's Health, A. D. H. B. (2012). *National Women's Annual Clinical Report 2011*. Auckland, New Zealand: National Women's Health, Auckland District Health Board. Retrieved from http://www.adhb.govt.nz/nwhealthinfo

North, R. A., McCowan, L. M., Dekker, G. A., Poston, L., Chan, E. H., Stewart, A. W., . . . Kenny, L. C. (2011). Clinical risk prediction for pre-eclampsia in nulliparous women: development of model in international prospective cohort. *BMJ, 342*, d1875.

Qiao, Q., Gao, W., Zhang, L., Nyamdorj, R., & Tuomilehto, J. (2007). Metabolic syndrome and cardiovascular disease. *Annals of Clinical Biochemistry, 44*(Pt 3), 232-263.

Rao, A. K., Daniels, K., El-Sayed, Y. Y., Moshesh, M. K., & Caughey, A. B. (2006). Perinatal outcomes among Asian American and Pacific Islander women. *American Journal of Obstetrics & Gynecology, 195*(3), 834-838.

Salmond, C., Crampton, P., & Atkinson, J. (2007). *NZDep2006 Index of Deprivation*. Wellington: University of Otago.

Shand, B., Elder, P., Scott, R., Poa, N., & Frampton, C. M. (2007). Comparison of plasma adiponectin levels in New Zealand Maori and Caucasian individuals. *New Zealand Medical Journal, 120*(1257), U2606.

Sibai, B., Dekker, G., & Kupferminc, M. (2005). Pre-eclampsia. *Lancet, 365*(9461), 785-799.

Sibai, B. M., Ewell, M., Levine, R. J., Klebanoff, M. A., Esterlitz, J., Catalano, P. M., . . . Joffe, G. (1997). Risk factors associated with preeclampsia in healthy nulliparous women. The Calcium for Preeclampsia Prevention (CPEP) Study Group. *American Journal of Obstetrics & Gynecology, 177*(5), 1003-1010.

Stone, P., Cook, D., Hutton, J., Purdie, G., Murray, H., & Harcourt, L. (1995). Measurements of blood pressure, oedema and proteinuria in a pregnant population of New Zealand. *Australian & New Zealand Journal of Obstetrics & Gynaecology, 35*(1), 32-37.

Swinburn, B. A., Ley, S. J., Carmichael, H. E., & Plank, L. D. (1999). Body size and composition in Polynesians. *International Journal of Obesity & Related Metabolic Disorders: Journal of the International Association for the Study of Obesity, 23*(11), 1178-1183.

Tam, C. Y., Hislop, G., Hanley, A. J., Minkin, S., Boyd, N. F., & Martin, L. J. (2011). Food, beverage, and macronutrient intakes in postmenopausal Caucasian and Chinese-Canadian women. *Nutrition and Cancer, 63*(5), 687-698.

Tanaka, M., Jaamaa, G., Kaiser, M., Hills, E., Soim, A., Zhu, M., . . . McNutt, L. A. (2007). Racial disparity in hypertensive disorders of pregnancy in New York State: a 10-year longitudinal population-based study. *American Journal of Public Health, 97*(1), 163-170.

World Health Organization expert consultation. (2004). Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet, 363*(9403), 157-163.

Chapter 10. | Ethnicity and Caesarean section

10.1. Preamble

The manuscript reproduced below was accepted for publication in The Australian and New Zealand Journal of Obstetrics and Gynaecology (ANZJOG) on the 10th November 2012 and is currently in press.

Permission

Reproduced from: Anderson N H, Sadler L C, Stewart A W, Fyfe E M, McCowan L M E. (2012). *Ethnicity and risk of Caesarean section in a term, nulliparous New Zealand obstetric cohort.* Australian & New Zealand Journal of Obstetrics & Gynaecology. 2013. 53(3)258-264.

Received 29 August 2012; accepted 10 November 2012.

10.2. Manuscript: Ethnicity and Caesarean section

Abstract

Background: One in four New Zealand (NZ) women undergo Caesarean Section (CS); however, little is understood about how ethnicity influences CS rates. Previous NZ studies do not include many of NZ's ethnic groups and have been unable to account comprehensively for clinical risk factors.

Aim: To investigate ethnicity as an independent risk factor for elective and emergency CS in nulliparous women at term. We hypothesised that compared with European, Māori and Pacific women would have a lower risk of elective CS, but there would be no ethnic differences in emergency CS.

Methods: This was a retrospective cohort analysis of prospectively recorded maternity data at National Women's Health, Auckland, NZ from 2006 to 2009. The study population was 11 848 singleton, nulliparous, term births. Multivariable logistic regression analysis was performed for elective and emergency CS, accounting for confounding factors.

Results: The overall CS rate was 31.2% (elective 7.8%, *n* = 923 and emergency 23.4%, *n* = 2770). Compared with European ethnicity, Pacific and Chinese women had a reduced odds of elective CS (adjusted odds ratios, aOR 0.42, [95% CI 0.24–0.73] and 0.68, [0.49–0.94], respectively), while Indian women had an increased odds of emergency CS (aOR 1.54, [1.26–1.88]). Rates of elective or emergency CS for other ethnicities were similar to European.

Conclusions: After adjustment for confounding, we report ethnic differences in elective and emergency CS rates, which may be related to patient and/or care provider factors. Further

prospective research is recommended to examine reasons for these ethnic differences in CS rates.

Introduction

Caesarean section (CS) is now the most commonly performed obstetric surgical intervention with one in four New Zealand (NZ) women being delivered by this procedure (Ministry of Health, 2011). Rates of CS have been observed to differ by ethnicity (Ibison, 2005; MacDorman, Menacker, & Declercq, 2008; Paranjothy, Frost, & Thomas, 2005; Thomas, Paranjothy, & Royal College of Obstetricians and Gynaecologists Clinical Effectiveness Support Unit, 2001; Vangen, Stoltenberg, Skrondal, Magnus, & Stray-Pedersen, 2000); however, there are limited NZ data comparing CS rates between women of different ethnicities. Studies investigating ethnic differences in CS rates have commonly assessed overall CS rates despite elective and emergency CS having substantially different clinical and patient risk factors (Braveman, Egerter, Edmonston, & Verdon, 1995; Chung et al., 2006; Jonas, Roder, & Chan, 1992; Kabir, Pridjian, Steinmann, Herrera, & Khan, 2005; Vangen et al., 2000). Additionally, although increased body mass index (BMI) is a well-established independent risk factor for emergency CS, few studies account for adiposity (Barau et al., 2006). This is particularly important when assessing ethnicity-related risk as obesity rates vary greatly between ethnicities (Ministry of Health, 2008). Previous NZ studies of CS have only investigated NZ's main ethnicities (Māori, Pacific and European) and have been limited by an inability to account for BMI as well as other important clinical confounders. These studies have shown lower CS rates in Māori and Pacific women compared with European (Harris et al., 2007; Sadler, McCowan, & Stone, 2002). As Māori and Pacific women are more likely to have higher risk pregnancies, it has been suggested that lower CS rates reflect ethnic inequalities in obstetric care (Harris et al., 2007). Other NZ studies have suggested structural discrimination exists in the health sector with patients treated differently based on ethnicity, often through unconscious bias, cultural misunderstandings, or uninformed beliefs (Human Rights Commission, 2012).

The decision for CS is a complex individualised process that involves an assessment of clinical risk along with patient and caregiver factors, including preference. Increasingly, patients have an expectation of choice regarding mode of delivery (Stjernholm, Petersson, & Eneroth, 2010) and this choice, along with improved procedural safety and a perceived 'normalisation' of Caesarean birth, has led to increasing numbers of requested CS. In Britain in 2000, a national audit found 'maternal request' to be the fifth most common indication for CS (Thomas et al., 2001). In contrast to elective CS, decision for emergency CS is less likely to be influenced by personal or caregiver preference as it should occur only in the presence of clinical indications.

Cultural considerations influence women's choices around birth and it follows that patient requested elective CS may differ by ethnicity. However, rates of emergency CS should not differ between ethnicities after accounting for confounding factors. The aim of our study was to investigate ethnicity as an independent contributor to elective and emergency CS in a term, nulliparous multi-ethnic population. We hypothesised that after adjusting for comprehensive clinical factors, including BMI, Māori and Pacific women would have a lower rate of elective CS compared with European, but there would be no difference in rates of emergency CS between ethnicities.

Materials and Methods

National Women's Health (NWH) is a tertiary referral service at Auckland City Hospital, Auckland, NZ with a multi-ethnic population and approximately 7500 maternities per year. The NWH clinical database of births from 2006 to 2009 was used for the present study, consisting of de-identified, prospectively collected maternity data for all births occurring at ≥ 20 weeks of gestation, including demographic data, antenatal complications, and detailed delivery and newborn data. Data are routinely checked for completeness, out of range values and inconsistency (National Women's Health, 2012). Ethical approval for this study was gained from the Northern X Regional Ethics Committee (NTX/09/179/EXP).

Inclusion criteria for this study were nulliparous women with singleton pregnancies n = 14 329. After exclusions (preterm birth <37 weeks of gestation, placenta praevia, stillbirth and major fetal congenital abnormality) the initial elective CS study population was n = 11 848, Figure 10.1. As an elective CS precludes an emergency CS, the 923 women who had an elective CS were removed for emergency CS analysis, leaving a study population of 10 925 women.

Elective CS was defined as any planned CS delivery regardless of onset of labour (National Women's Health, 2012). Therefore, a CS scheduled prior to labour but performed after the onset of labour was considered elective. Emergency CS was defined as any CS that occurred because of an emergency situation (e.g. fetal distress) either pre-labour or in labour, when CS had not been previously considered necessary (National Centre for Classification in Health, 2004; National Women's Health, 2012).

Confounding factors considered *a priori* for both elective and emergency CS were as follows: ethnicity, BMI, maternal age, socio-economic status, caregiver, use of artificial reproductive technologies, diabetes (Hoffman, Nolan, Wilson, Oats, & Simmons, 1998), presentation at delivery, small for gestational age and large for gestational age infants (defined as a birthweight <10th and >90th customised centile (Anderson, Sadler, Stewart, & McCowan, 2012)), birthweight and gestation at delivery (determined by the Australasian Society for Ultrasound in Medicine guidelines (Australasian Society for Ultrasound in Medicine, 2001-2007a, 2001-

2007b)). Additional *a priori* confounding factors for emergency CS were as follows: maternal height, hypertensive disease (Brown, Lindheimer, de Swiet, Van Assche, & Moutquin, 2001), antepartum haemorrhage (APH) and induction of labour (IOL).

Ethnicity was self-determined and prioritised as per NZ Ministry of Health guidelines (Ministry of Health, 2004). Other Asian ethnicity included women from South-East Asia, the Indian subcontinent (excluding India), Japan and Korea. Maternal height and weight were measured and recorded at the first antenatal booking visit and BMI was calculated as weight (in kg) divided by height (in metres) squared. Socio-economic status was estimated using a centile score (range 1–10) based on residential area deprivation data from the 2006 NZ census (NZDep2006) (Salmond, Crampton, & Atkinson, 2007). Centile scores were condensed into quintiles (range 1–5) without change in statistical significance, where quintile 1 represented the least deprived residential areas and deprivation quintile 5 the most deprived areas.

Caregiver was defined as the lead maternity carer at birth, and was composed of independent midwives (IMW), private obstetricians, general practitioners (GP) and public (hospital-based) midwives. In NZ women deliver at public hospitals, and maternity care that is provided by IMW, GPs and public midwives is free. In contrast, for private obstetric specialist care the woman pays a fee that is not usually covered through health insurance. Private obstetricians care for their women throughout labour independently of the public teams.

Statistical Methods:

Univariable analysis of categorical data was performed using the chi squared test. A *P*-value <0.05 was considered significant. Crude and adjusted odds ratios (OR and aOR) with 95% CI were calculated using simple and multivariable logistic regression, with all *a priori* confounding factors included in the multivariable logistic regression model.

All statistical tests were performed using SAS© version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

The overall CS rate in our eligible study population of 12 845 nulliparous women delivering at term was 31.0% (elective CS 7.7%, *n* = 984 and emergency CS 23.3%, *n* = 2999). After exclusion of women with missing data, the CS rate in the elective CS study population of 11 848 women was 31.2% (elective 7.8%, *n* = 923 and emergency 23.4%, *n* = 2770). More than half of the study population were of European ethnicity (*n* = 6147, 51.9%) followed by Chinese (*n* = 1753, 14.8%), Pacific (*n* = 1171, 9.9%), Indian (*n* = 880, 7.4%) and Māori ethnicity (*n* = 710, 6.0%), Table 10.1. The greatest proportion of women were under IMW care (*n* = 5549, 46.8%), public

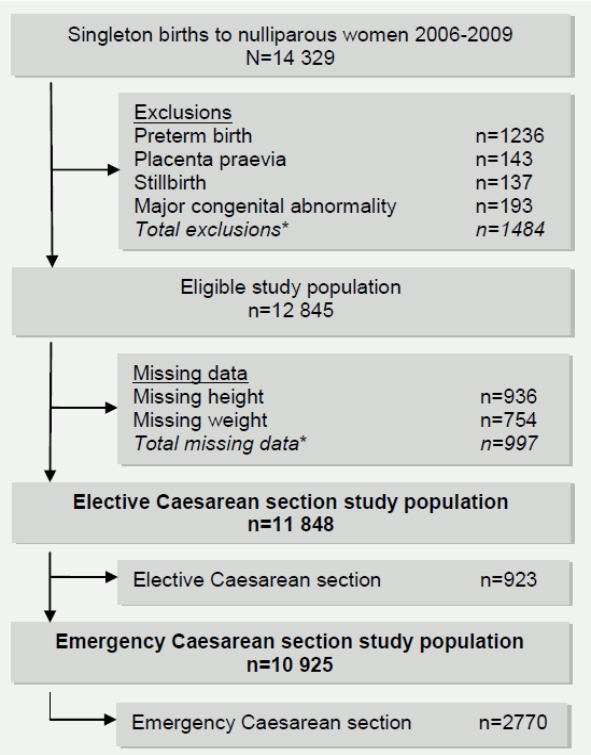


Figure 10.1. Flowchart of participants
*** Each participant may have more than one exclusion or missing data, so numbers do not total**

hospital teams and private obstetricians each cared for approximately a quarter of all women (*n* = 3228, 27.2% and *n* = 2838, 24.0% respectively), and only 2% (*n* = 233) of women were under GP care, Table 10.1.

Elective Caesarean

The majority of elective CS were performed in European women (*n* = 676, 73.2%) and correspondingly they had the highest rate of elective CS at 11.0%, Table 10.2. In contrast, Māori and Pacific women had the lowest rates of elective CS at 2.8% (*n* = 20) and 2.1% (*n* = 25) respectively.

Crude and adjusted odds ratios for elective CS are presented in Table 10.2. Increased or decreased crude odds for elective CS were observed with all *a priori* confounding factors except BMI. In particular, crude odds for elective CS were reduced in all ethnicities compared with European. After adjustment for confounding, Pacific and Chinese women had a lower odds of elective CS compared to European women (aOR 0.42, [95% CI 0.24–0.73] and 0.68, [0.49–0.94] respectively), private obstetric care was associated with a four-fold increased odds of elective CS compared with public care (aOR 4.02, [3.01–5.36]), and for every 5years of increasing maternal age there was a 67% increase in odds of CS (aOR 1.67, [1.52–1.85]), Table 10.2.

Table 10.1. Lead maternity carer by ethnicity for full cohort (*P* <0.01).

	Total *n*	Public *n* (%)	IMW *n* (%)	GP *n* (%)	Private *n* (%)
Total	11 848	3228 (27.2)	5549 (46.8)	233 (2.0)	2838 (24.0)
European	6147	894 (14.5)	2869 (46.7)	136 (2.2)	2248 (36.6)
Māori	710	314 (44.2)	335 (47.2)	8 (1.1)	53 (7.5)
Pacific	1171	735 (62.8)	391 (33.4)	13 (1.1)	32 (2.7)
Chinese	1753	259 (14.8)	1235 (70.5)	45 (2.5)	214 (12.2)
Indian	880	479 (54.4)	269 (30.6)	11 (1.3)	121 (13.7)
Other Asian	841	363 (43.1)	354 (42.1)	13 (1.6)	111 (13.2)
Other	346	184 (53.2)	96 (27.7)	7 (2.0)	59 (17.1)

IMW, Independent midwife
GP, General practitioner

Emergency CS

Of the 2770 emergency CS, 6.2% (*n* = 172) were carried out before the onset of labour. Women of Indian ethnicity had the highest rate of emergency CS at 29.7% (*n* = 247) while Māori and Pacific women had the lowest rates at 19.7% (*n* = 136) and 20.6% (*n* = 236) respectively, Table 10.3. Rates of emergency CS varied by care provider with the lowest rate in public care (21.7%, *n* = 671) and the highest with private obstetric care (34.8%, *n* = 780).

After adjustment for confounding, women of Indian and Other ethnicities had increased odds of emergency CS (aOR 1.54, [1.26–1.88] and 1.45, [1.09–1.91] respectively) compared with European women, Table 10.3. Women of Other Asian ethnicity had a borderline increase in odds (aOR 1.24, [1.01–1.51]). Māori, Pacific and Chinese women had no difference in odds of emergency CS compared to European. Other factors associated with increased emergency CS rates were increasing BMI and increasing maternal age as well as IMW and private obstetric care compared with public care, Table 10.3.

As high socio-economic status is strongly correlated with private obstetric care, subgroup multivariable analyses were performed for both elective CS and emergency CS populations where women with private obstetric care were excluded. In both subgroup analyses aORs were minimally changed, with no change in statistical significance of other variables in the model (data not shown). Both deprivation quintile and caregiver remained in the final multivariable models as both were *a priori* confounding factors.

Table 10.2. Characteristics of study population by elective Caesarean section (CS) status, with crude and adjusted odds ratios (OR, [95%CI]) for elective CS

	Elective CS		No-elective CS		Crude		Adjusted*		
	n = 923	7.8%	*n* = 10 925	92.2%	OR [95% CI]		OR [95% CI]		*P*-value†
Maternal ethnicity									
European	676	73.2	5471	50.1	Ref		Ref		<0.01
Māori	20	2.2	690	6.3	0.24	[0.15, 0.37]	0.68	[0.38, 1.21]	
Pacific	25	2.7	1146	10.5	0.18	[0.12, 0.27]	0.42	[0.24, 0.73]	
Chinese	77	8.3	1676	15.3	0.37	[0.29, 0.47]	0.68	[0.49, 0.94]	
Indian	47	5.1	833	7.6	0.46	[0.34, 0.62]	1.01	[0.67, 1.52]	
Other Asian	56	6.1	785	7.2	0.58	[0.44, 0.77]	1.39	[0.96, 2.00]	
Other ethnicity	22	2.4	324	3.0	0.55	[0.35, 0.85]	1.09	[0.62, 1.93]	
BMI‡ (kg/m^2)	24.2	(4.9)	24.5	(5.3)	0.96	[0.90, 1.02]	1.02	[0.92, 1.14]	0.68
Maternal age‡ (years)	33.6	(5.1)	29.3	(5.6)	2.14	[1.99, 2.29]	1.67	[1.52, 1.85]	<0.01
Deprivation quintile (NZDep2006)									
1	253	27.4	1743	16.0	Ref		Ref		0.13
2	214	23.2	2178	19.9	0.68	[0.56, 0.82]	0.86	[0.67, 1.10]	
3	208	22.5	2493	22.8	0.58	[0.47, 0.70]	0.91	[0.71, 1.17]	
4	140	15.2	2431	22.3	0.40	[0.32, 0.49]	0.68	[0.51, 0.91]	
5	108	11.7	2080	19.0	0.36	[0.28, 0.45]	0.90	[0.66, 1.24]	
Care									
Public	135	14.6	3093	28.3	Ref		Ref		<0.01
Independent Midwife	184	19.9	5365	49.1	0.79	[0.63, 0.99]	0.51	[0.37, 0.69]	
General practitioner	7	0.8	226	2.1	0.71	[0.33, 1.54]	0.32	[0.11, 0.90]	
Private obstetrician	597	64.7	2241	20.5	6.10	[5.02, 7.41]	4.02	[3.01, 5.36]	

Data presented are *n* % for categorical variables, mean (SD) for continuous variables and OR [95% CI] as appropriate.
***Adjusted ORs are adjusted for all variables in the table as well as artificial reproductive technology, diabetes status, presentation at delivery, small for gestational age, large for gestational age, birthweight and gestation at delivery.**
† Chi squared *P*-value for adjusted model
‡ORs and 95%CI presented for BMI ↑ 5 units, and maternal age ↑ 5 years

Discussion

We report that ethnicity is independently associated with both elective and emergency CS in nulliparous women at term, specifically a reduced rate of elective CS in Pacific and Chinese women, and an increased rate of emergency CS in Indian and Other ethnicity compared with European women.

Elective CS

Rates of elective CS are increasing globally (MacDorman et al., 2008; Meikle, Steiner, Zhang, & Lawrence, 2005; Stjernholm et al., 2010) including in Australia (Stavrou, Ford, Shand, Morris, & Roberts, 2011) and NZ (National Women's Health, 2012) and particularly among more affluent and older nulliparous women (Alves & Sheikh, 2005; Ecker, Chen, Cohen, Riley, & Lieberman, 2001). These increases are not explained by increasing obstetric risk and are likely to reflect either differences in clinical decision making or CS on maternal request (Stavrou et al., 2011; Stjernholm et al., 2010).

Table 10.3. Characteristics of study population by emergency Caesarean section (CS) status, with crude and adjusted odds ratios (OR, [95%CI]) for emergency CS

	Emergency CS		No-emergency CS		Crude		Adjusted*		
	n = 2770	25.4%	*n* = 8155	74.6%	OR [95% CI]		OR [95% CI]		*P*-value†
Maternal ethnicity									
European	1484	53.6	3987	48.9	Ref		Ref		<0.01
Māori	136	4.9	554	6.8	0.66	[0.54, 0.80]	1.10	[0.87, 1.38]	
Pacific	236	8.5	910	11.2	0.70	[0.60, 0.81]	1.08	[0.88, 1.32]	
Chinese	362	13.1	1314	16.1	0.74	[0.65, 0.84]	1.03	[0.88, 1.20]	
Indian	247	8.9	586	7.2	1.13	[0.97, 1.33]	1.54	[1.26, 1.88]	
Other Asian	213	7.7	572	7.0	1.00	[0.85, 1.18]	1.24	[1.01, 1.51]	
Other ethnicity	92	3.3	232	2.8	1.07	[0.83, 1.37]	1.45	[1.09, 1.91]	
BMI‡ (kg/m^2)	25.3	(5.7)	24.2	(5.0)	1.23	[1.18, 1.28]	1.24	[1.18, 1.31]	<0.01
Maternal age‡ (years)	31.1	(5.3)	28.8	(5.6)	1.48	[1.42, 1.54]	1.46	[1.39, 1.54]	<0.01
Deprivation quintile (NZDep2006)									
1	500	18.1	1243	15.3	Ref		Ref		0.33
2	593	21.4	1585	19.5	0.93	[0.81, 1.07]	0.98	[0.84, 1.15]	
3	618	22.3	1875	23.0	0.82	[0.71, 0.94]	0.89	[0.76, 1.04]	
4	616	22.3	1815	22.3	0.84	[0.74, 0.97]	0.92	[0.78, 1.08]	
5	440	15.9	1632	20.0	0.67	[0.58, 0.78]	0.86	[0.73, 1.03]	
Care									
Public	671	24.2	2422	29.7	Ref		Ref		<0.01
Independent midwife	1260	45.5	4105	50.3	1.11	[1.00, 1.23]	1.21	[1.06, 1.38]	
General practitioner	59	2.1	167	2.1	1.28	[0.94, 1.74]	1.33	[0.94, 1.87]	
Private obstetrician	780	28.2	1461	17.9	1.93	[1.71, 2.18]	1.87	[1.60, 2.19]	

Data presented are *n* % for categorical variables, mean (SD) for continuous variables and OR [95% CI] as appropriate.

***Adjusted ORs are adjusted for all variables in the table as well as maternal height, artificial reproductive technology, diabetes status, hypertensive disease, antepartum haemorrhage, presentation at delivery, induction of labour, small for gestational age, large for gestational age, birthweight and gestation at delivery.**

† Chi squared *P*-value for adjusted model

‡ORs and 95%CI presented for BMI ↑ 5 units, and maternal age ↑ 5 years

Our study in term nulliparous women accounted for known clinical indications/ confounders of elective CS and therefore non-clinical patient and/or provider factors are likely to be the major determinants for elective CS in this study population. This assumption is reinforced by the older age of women who underwent elective CS, as well as the high proportion of elective CS performed by private obstetricians, Table 10.2. Elective CS on request is discouraged in the NZ public health system and as a result is difficult to access. In contrast, women who can afford private obstetric care can access elective CS through patient request or through CS being offered as an alternative method of delivery, helping to explain why nearly two-thirds of elective CS were performed by private obstetricians. Our finding of an independently reduced rate of elective CS in Pacific women compared to European (aOR 0.42, [0.24–0.73]) is consistent with previous findings (Sadler et al., 2002). Although non-significant, the low odds ratio point estimate for elective CS in Māori (aOR 0.68, [0.38–1.21]) raises the possibility that Māori women may also have a lower rate of elective CS than European women. Few Māori and Pacific women (7.5% and 2.7% respectively) were cared for by private obstetricians (Table 10.1), likely reflecting both choice and affordability as both Māori and Pacific women are more likely than

European women to live in deprived areas (Ministry of Health, 2010; Tobias, Bhattacharya, & White, 2008). However, this reduction in rate of elective CS in Pacific women (and a trend in Māori women) was present even after adjusting for socioeconomic deprivation, and may reflect a cultural preference for a midwifery model of care (public hospital and independent midwife care) and vaginal birth. Equally Māori and Pacific women may be subject to provider bias and not be offered the choice of private obstetric care. We also observed a reduced rate of elective CS in Chinese women (aOR 0.68, [0.49–0.94]) which may also reflect a lack of choice regarding private obstetric care, or a cultural preference for a midwifery model of care and vaginal birth. Over 70% of Chinese women chose IMW care, with 12% choosing private obstetric care, Table 10.1. As Asian peoples have similar deprivation indices to European (Ministry of Health, 2010; Tobias et al., 2008), this preference of caregiver is more likely to be related to cultural factors rather than affordability.

As data on indication for CS at NWH are not routinely checked for accuracy, we are not able to comment further on reasons for elective CS. It is likely that small numbers of medically indicated elective CS are present in this study population (for example, maternal medical conditions such as HIV and cardiac conditions); however, it is doubtful this would significantly influence our results.

Emergency CS

In contrast to elective CS, emergency CS is generally performed on the basis of clinical need, and should be independent of non-clinical patient and carer factors. After adjusting for known associations for emergency CS, nulliparous women of Māori and Pacific ethnicity had the same chance of emergency CS as European women, consistent with findings from one previous study (Sadler et al., 2002). This finding is reassuring in the face of poorer perinatal outcomes among Māori and Pacific women, and suggests these adverse outcomes are unlikely to be related to differential rates of emergency CS. Additionally, as increasing CS rates do not improve perinatal outcomes in developed countries (Villar et al., 2006), there is also no evidence of systematic over-intervention in Māori and Pacific women in our cohort. Other investigators that found Māori women to have lower emergency CS rates compared with non-Māori suggested an ethnic disparity in obstetric care (Harris et al., 2007); however, this previous study used national coding data that did not contain major demographic or clinical confounders such as parity, BMI, infant birthweight or IOL. As our study was limited to term nulliparous women in one centre, we cannot exclude a relationship between emergency CS and Māori ethnicity in the whole NZ obstetric population.

Women of Indian ethnicity were found to have independently increased rates of emergency CS compared with European. In addition, we found a borderline increase in emergency CS for Other Asian women, which included women from South Asia such as Bangladesh, Pakistan and Sri

Lanka. Studies of CS rates in Indian /South Asian women from the UK (a comparable European multi-cultural population) are conflicting (Ibison, 2005; Paranjothy et al., 2005; Thomas et al., 2001), and interpretation is limited as BMI was not included in these analyses. Reasons for increased rates of emergency CS in Indian / South Asian women are unclear and further research is required to investigate this finding.

A strength of our study is the separate analyses of elective and emergency CS. Women who have an elective CS have substantially different characteristics to women who have either a vaginal birth or emergency CS and should be analysed separately. Removing these women minimises any potential bias this group may have when investigating emergency CS.

We chose to investigate nulliparous women only, as decisions around birth in parous women are heavily influenced by experiences with previous births, particularly a previous CS birth. In addition we excluded preterm births, as they are by definition pathological and mode of delivery is generally a clinical decision that should not differ by ethnicity. As a result, women with preterm birth do not usually have the option of choosing an elective CS, and therefore analyses of elective CS that include preterm births will be biased. For completeness, a multivariable sub-analysis of the nulliparous women who were excluded with preterm birth in this study was performed (n = 1236 preterm births, n = 723 with complete data) and there was no significant ethnicity effect on risk of CS (P = 0.07, data not shown).

Rates of CS differ between maternity units throughout NZ which may reflect local differences in practice, obstetric risk as well as access to private obstetric care. Our study was performed in a large tertiary referral centre in Auckland, New Zealand, which has a relatively large number of private obstetric practitioners. Women in smaller centres may not have access to private obstetric care however as we have adjusted for caregiver as a confounder of CS, we believe these results are generalisable to nulliparous women in other settings.

Conclusions

This study in NZ nulliparous women at term is the first detailed analysis of ethnic differences in elective and emergency CS that includes comprehensive clinical risk factors. We report an independent reduction in elective CS rates in Pacific and Chinese ethnicities which are likely to be related to non-clinical patient and/or care provider factors, and increased rates of emergency CS in Indian, Other Asian and Other ethnicities compared with European ethnicity. Further prospective research is recommended to examine reasons for these ethnic differences in CS rates.

References

Alves, B., & Sheikh, A. (2005). Investigating the relationship between affluence and elective caesarean sections. *BJOG: An International Journal of Obstetrics & Gynaecology, 112*(7), 994-996.

Anderson, N., Sadler, L., Stewart, A., & McCowan, L. (2012). Maternal and pathological pregnancy characteristics in customised birthweight centiles and identification of at-risk small-for-gestational-age infants: a retrospective cohort study. *BJOG, 119*(7), 848-856.

Australasian Society for Ultrasound in Medicine. (2001-2007a). Guidelines for the mid trimester obstetric scan *Policies and Statements D2*. http://www.asum.com.au/site/policies.php: ASUM.

Australasian Society for Ultrasound in Medicine. (2001-2007b). Statement on normal ultrasonic fetal measurements *Policies and Statements D7*. http://www.asum.com.au/site/policies.php: ASUM.

Barau, G., Robillard, P. Y., Hulsey, T. C., Dedecker, F., Laffite, A., Gerardin, P., & Kauffmann, E. (2006). Linear association between maternal pre-pregnancy body mass index and risk of caesarean section in term deliveries. *BJOG, 113*(10), 1173-1177.

Braveman, P., Egerter, S., Edmonston, F., & Verdon, M. (1995). Racial/ethnic differences in the likelihood of cesarean delivery, California. *American Journal of Public Health, 85*(5), 625-630.

Brown, M. A., Lindheimer, M. D., de Swiet, M., Van Assche, A., & Moutquin, J. M. (2001). The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). *Hypertension in Pregnancy, 20*(1), IX-XIV.

Chung, J. H., Garite, T. J., Kirk, A. M., Hollard, A. L., Wing, D. A., & Lagrew, D. C. (2006). Intrinsic racial differences in the risk of cesarean delivery are not explained by differences in caregivers or hospital site of delivery. *American Journal of Obstetrics & Gynecology, 194*(5), 1323-1328.

Ecker, J. L., Chen, K. T., Cohen, A. P., Riley, L. E., & Lieberman, E. S. (2001). Increased risk of cesarean delivery with advancing maternal age: indications and associated factors in nulliparous women. *American Journal of Obstetrics & Gynecology, 185*(4), 883-887.

Harris, R., Robson, B., Curtis, E., Purdie, G., Cormack, D., & Reid, P. (2007). Maori and non-Maori differences in caesarean section rates: a national review. *New Zealand Medical Journal, 120*(1250), U2444.

Hoffman, L., Nolan, C., Wilson, J. D., Oats, J. J., & Simmons, D. (1998). Gestational diabetes mellitus--management guidelines. The Australasian Diabetes in Pregnancy Society (updated Dec 2002). *Medical Journal of Australia, 169*(2), 93-97.

Human Rights Commission. (2012). *A fair go for all? Rite tahi tātou katoa? Addressing Structural Discrimination in Public Services*. New Zealand: Human Rights Commission.

Ibison, J. M. (2005). Ethnicity and mode of delivery in 'low-risk' first-time mothers, East London, 1988-1997. *European Journal of Obstetrics, Gynecology, & Reproductive Biology, 118*(2), 199-205.

Jonas, O., Roder, D., & Chan, A. (1992). The association of maternal and socioeconomic characteristics in metropolitan Adelaide with medical, obstetric and labour complications and pregnancy outcomes. *Australian & New Zealand Journal of Obstetrics & Gynaecology, 32*(1), 1-5.

Kabir, A. A., Pridjian, G., Steinmann, W. C., Herrera, E. A., & Khan, M. M. (2005). Racial differences in cesareans: an analysis of U.S. 2001 National Inpatient Sample Data. *Obstetrics & Gynecology, 105*(4), 710-718.

MacDorman, M. F., Menacker, F., & Declercq, E. (2008). Cesarean birth in the United States: epidemiology, trends, and outcomes. *Clinics in Perinatology, 35*(2), 293-307.

Meikle, S. F., Steiner, C. A., Zhang, J., & Lawrence, W. L. (2005). A national estimate of the elective primary cesarean delivery rate. *Obstetrics & Gynecology, 105*(4), 751-756.

Ministry of Health. (2004). *Ethnicity Data Protocols for the Health and Disability Sector*. Wellington: Ministry of Health. Retrieved from http://www.nzhis.govt.nz/documentation/ethnicity/index.html

Ministry of Health. (2008). A Portrait of Health. Key Results of the 2006/07 New Zealand Health Survey. Wellington: Ministry of Health.

Ministry of Health. (2010). Living Standards and Health: New Zealand 2006/07. Wellington: Ministry of Health.

Ministry of Health. (2011). Maternity Snapshot 2010. from http://www.health.govt.nz/publication/maternity-snapshot-2010-provisional-data

National Centre for Classification in Health. (2004). *The International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modificaiton (ICD-10-AM). Volumes 1-5* (Fourth edition ed., Vol. 5). Sydney: National Centre for Classification in Health.

National Women's Health, A. D. H. B. (2012). *National Women's Annual Clinical Report 2011*. Auckland, New Zealand: National Women's Health, Auckland District Health Board. Retrieved from http://www.adhb.govt.nz/nwhealthinfo

Paranjothy, S., Frost, C., & Thomas, J. (2005). How much variation in CS rates can be explained by case mix differences? *BJOG: An International Journal of Obstetrics & Gynaecology, 112*(5), 658-666.

Sadler, L. C., McCowan, L. M. E., & Stone, P. (2002). Associations between ethnicity and obstetric intervention in New Zealand.[erratum appears in N Z Med J 2002 Feb 22;115(1148):86]. *New Zealand Medical Journal, 115*(1147), 36-39.

Salmond, C., Crampton, P., & Atkinson, J. (2007). *NZDep2006 Index of Deprivation*. Wellington: University of Otago.

Stavrou, E. P., Ford, J. B., Shand, A. W., Morris, J. M., & Roberts, C. L. (2011). Epidemiology and trends for Caesarean section births in New South Wales, Australia: a population-based study. *BMC Pregnancy & Childbirth, 11*, 8.

Stjernholm, Y. V., Petersson, K., & Eneroth, E. (2010). Changed indications for cesarean sections. *Acta Obstetricia et Gynecologica Scandinavica, 89*(1), 49-53.

Thomas, J., Paranjothy, S., & Royal College of Obstetricians and Gynaecologists Clinical Effectiveness Support Unit. (2001). *National Sentinel Caesarean Section Audit Report*. RCOG Press: Royal College of Obstetricians and Gynaecologists.

Tobias, M., Bhattacharya, A., & White, P. (2008). Cross classification of the New Zealand population by ethnicity and deprivation: trends from 1996 to 2006. *Australian and New Zealand Journal of Public Health, 32*(5), 431-436.

Vangen, S., Stoltenberg, C., Skrondal, A., Magnus, P., & Stray-Pedersen, B. (2000). Cesarean section among immigrants in Norway. *Acta Obstetricia et Gynecologica Scandinavica, 79*(7), 553-558.

Villar, J., Valladares, E., Wojdyla, D., Zavaleta, N., Carroli, G., Velazco, A., . . . perinatal health research, g. (2006). Caesarean delivery rates and pregnancy outcomes: the 2005 WHO global survey on maternal and perinatal health in Latin America. *Lancet, 367*(9525), 1819-1829.

Chapter 11. |Discussion and Conclusions

11.1. Overview

This chapter will provide a summary of the publications in the previous chapters, with a critique of methods and results, limitations of the studies with an expansion of the discussions. There will be a discussion of the implications of the research findings and consideration of future directions to expand and/or clarify the findings of these analyses. This chapter will conclude with an overall summary of the thesis.

11.2. Birthweight

The impact of ethnicity and obesity on birthweight were investigated in Chapter 6 and Chapter 7. In Chapter 6 the ethnicity-related impact on birthweight was observed through the recalculation of the NZ customised birthweight centiles, and the value of including maternal characteristics (including height and weight) in a customised birthweight model was confirmed. In Chapter 7, it was observed that contrary to published risk factors for SGApop, obesity was not protective of SGAcust but instead was an independent risk factor.

11.2.1. Customised birthweight centiles

As discussed in section 5.3.1 and Chapter 6, although the previous NZ customised birthweight model better identified at-risk infants than a population-based birthweight reference, there were data limitations that may have introduced bias into the early model. As a result it was timely to recalculate birthweight centile coefficients with modern demographic data, as well as including adjustment for important pathological influences on birthweight. The new model was able to include ethnicity coefficients for 16 ethnicities, compared with six ethnicities in the previous model. Formal testing suggests that the new model better identifies infants at-risk of perinatal death than the old model although the overall performance of the models was similar. Further, we published data showing that compared to an ultrasound-based fetal weight reference, the inclusion of maternal characteristics and exclusion of pathological influences on birthweight increased the detection of SGA infants at-risk of perinatal death in our population, which is multiethnic with high rates of overweight and obesity.

A limitation of these analyses is that the majority of infants who comprised the study population for SGA-related adverse outcomes were the same infants on whom the birthweight coefficients were created (in both the SGAus versus SGAfull and SGAold versus SGAnew analyses). In fact 93% of infants were included in both centile creation and outcome analyses. Ideally independent cohorts of infants would be used at each step, although this would require a much greater sample than was available. In addition, perinatal death is a rare event (in NZ 10.1:1000 total births (PMMRC, 2012)) and subgroup analyses of infants who changed classifications between

models had small numbers (e.g. SGAus only *n = 676* and SGAfull only *n* = 888, Table 6.3) meaning results should be interpreted with caution and ideally confirmed in a larger dataset. However our finding of a substantially increased risk of perinatal death among SGAfull only infants (RR 4.7, 95% CI 2.7–7.9) and no increased risk among SGAus only (RR 1.1, 95% CI 0.4–3.6) suggest a true difference between these groups, supported by a significant increase in overall odds of perinatal death among SGAfull compared with SGAus infants (*P* = 0.02).

As mentioned above, the value of our study of birthweight customisation lies in the use of a population that has a large amount of variation in maternal characteristics such as ethnic diversity and increased rates of obesity. Previous analyses of customised birthweight models have been limited by populations with predominantly homogenous maternal characteristics, i.e. a predominant single ethnicity with little variation in height and weight (Hutcheon et al., 2008; Hutcheon et al., 2011; Mikolajczyk et al., 2011). Hutcheon and colleagues (Hutcheon et al., 2008) specifically aimed to compare the Gardosi method of customisation to an ultrasound fetal weight model but used a customised birthweight model that was different from that of Gardosi and colleagues (no adjustment for pathological variables and maternal characteristic variables were categorised where the Gardosi model used continuous variables) and was limited by the previously mentioned homogenous Swedish cohort. Their finding of no improvement in performance of their customised model over the ultrasound model is likely limited by both their population and their customisation method, leading to underestimation of the influence of maternal characteristics in birthweight customisation. A further study by Mikolajczyk and colleagues used the Gardosi 'proportionality' concept (see Appendix 2) and applied this to global populations (Mikolajczyk et al., 2011). Importantly, they found not only that the Hadlock ultrasound fetal weight reference (developed from a European cohort) grossly overestimated rates of SGA among many populations, but that adjustment for 'country' (the mean term birthweight of that population) substantially improved identification of SGA infants at-risk of perinatal death. The countries involved in this study were non-European and again predominantly homogenous, meaning the mean birthweight adjustment can be considered a surrogate adjustment for both the ethnic effect on birthweight as well as the mean maternal characteristics (height, weight and parity) of the population. Although they mention that further addition of individual characteristics to this 'country' adjusted model did not further improve the detection of at-risk SGA infants, this can be explained by the surrogate adjustment, as described. These findings by Mikolajczyk and colleagues therefore support our findings that maternal characteristics have additional value when incorporated into customised birthweight models.

It is important to comment on the overall RRs of preterm birth and perinatal death in the new NZ customised birthweight model compared with the old model, Figure 6.3. Although the rate of

perinatal death among newly diagnosed SGA infants (New SGA) was higher than among both non-SGA infants (1.2% compared with 0.4%, RR 2.98 95% CI 1.39–6.41, Table 6.6), this came at a cost of classifying an additional 603 infants as SGA to identify seven perinatal deaths. As a result, although the RR of perinatal death for SGAnew infants was similar to the RR for SGAold infants, it was slightly lower (SGAnew RR 9.4, 95% CI 7.1–12.4, SGAold RR 10.2, 95% CI 7.8–13.4, Figure 6.3). Additionally, preterm birth rates were not different in the newly diagnosed SGAnew infants compared with non-SGA infants (5.6% compared with 5.8%, RR 1.15 95% CI 0.79–1.71, Table 6.6), and so the inclusion of additional SGAnew infants also slightly reduced the RR of preterm birth compared with SGAold infants (SGAnew RR 2.7, 95% CI 2.4–2.9, SGAold RR 3.0, 95% CI 2.7–3.3, Figure 6.3). Overall we consider the better quality data and improvements of the new model mean it is superior to the old model. Applying the new birthweight model to detection of SGA in NZ will have an impact on healthcare resources as approximately 2.5% more infants will be identified as SGA after birth. Assuming approximately 50% of SGA infants are detected antenatally (through the use of customised antenatal growth chart, see section 5.3 above) (Roex et al., 2012), approximately 1.25% additional women will be referred for antenatal investigation compared with the old model.

Subsequent to the publication of these analyses (Chapter 6) the new NZ birthweight coefficients have been incorporated into a freely available download of the GROW software, produced by the UK Gestation Network, administered by the Perinatal Institute (Gardosi & Francis, 2012a, 2012b). It is currently available for use both nationwide and internationally. The new model has also been incorporated into the NWH electronic database, which has the above software embedded into the routine electronic patient record (Healthware NET version 6.0.0.3, Healthcare group CSC).

11.2.2. Risk factors for small for gestational age infants

In chapter seven we performed the first comprehensive analysis of clinical risk factors for customised SGA in a general obstetric population. Previously in this thesis the physiological and pathological determinants of fetal growth have been discussed (Chapter 5), with the observation that studies of SGA have predominantly used population birthweight references to define smallness. As over 70% of infants are small by both population and customised birthweight standards, it is expected there will be a substantial overlap of risk factors between the two standards. However, since customised birthweight standards account for known physiological influences on birthweight, it is also expected there will be differences in risk factors that predominantly relate to maternal characteristics. Our study is the first comprehensive analysis of independent risk factors for SGA among a general obstetric cohort.

Consistent with our hypothesis we observed that obesity is not protective of SGAcust, but instead is an important risk factor. We also confirmed well-established risk factors for SGApop

are also risk factors for SGAcust, including smoking, hypertensive disease APH and pre-existing medical conditions. Older maternal age, which has been inconsistently associated with SGApop (section 5.2.2), was also found to be a risk factor for SGAcust in our population. In contrast, socioeconomic status, was not associated with SGAcust. Even after accounting for physiologically lower birthweights among nulliparous women, we found that nulliparity was still a risk factor for SGAcust. This finding therefore suggests that nulliparity has both a physiological and pathological influence on birthweight helping to explain the opposing views of previous researchers (see section 5.2.1 parity). Finally, despite univariate associations between SGAcust and various ethnicities that suggested differences in rates of SGA up to 40% compared with European ethnicity, these can be completely explained by other pathological associations such as smoking, hypertensive disease and obesity.

Again, our SGA analyses were performed in a dataset where 92%[5] of infants had been used to create the customised birthweight coefficients. These findings should be confirmed in an independent obstetric cohort with comprehensive BMI and clinical data and where there is similar ethnic diversity. In addition, this retrospective database analysis was unable to include other associations with birthweight such as gestational weight gain, caffeine intake, alcohol and illicit substances, diet, multivitamin use, first trimester bleeding etc. (described in Chapter 5).

As discussed previously, the birthweight customisation model adjusts for well-established influences on birthweight. As a result there are some variables that are used in the customised birthweight model that are also included in SGA analyses. With regards to pathological factors, there is prior established knowledge that hypertensive disease, diabetes, APH and smoking have a negative influence on fetal growth and so the calculation of the optimal customised birthweight deliberately excludes these factors. As a result, an association between these pathological factors and SGA is expected. This analysis adds to this prior knowledge by allowing the magnitude of risk to be estimated for each of these pathological features. Additionally, birthweight customisation has already accounted for physiological influences on birthweight (ethnicity, height, weight and parity) therefore any further association with SGA must be over-and-above the physiological association, and is therefore an independent risk factor. For example, in the case of nulliparity, even after an adjustment for the lower birthweights observed among nulliparous women, these women still have higher rates of SGA infants, meaning this association is additional to the physiological association with birthweight i.e. a pathological risk factor. The same rationale applies to the independent association between obesity and SGA. An association between obesity and SGAcust has been independently observed both in an

[5] A difference of *n* = 278 exists in study populations between chapter 6 (*n* = 25 976) and chapters 7 and 9 (*n* = 26 254) due to the inclusion of women with missing smoking data in the later analyses. Sensitivity analyses of these women showed that they had a similar relationship to each outcome (SGA and pre-eclampsia) as non-smokers, and were included into SGA and pre-eclampsia analyses as non-smokers.

Australian population where a multivariable analysis of limited clinical factors was performed (McIntyre et al., 2012), and in a subgroup analysis of the previously mentioned Swedish cohort (although no multivariable analysis accompanied this report) (Gardosi et al., 2009).

As ethnic-specific BMI is not a widely used classification, we elected to repeat our analyses using WHO BMI criteria. As illustrated in Figure 7.2, rates of SGA were similar between each BMI criterion and the overall independent odds of SGA for obese women compared with normal weight remained similar (ethnic-specific obesity aOR 1.24, 95% CI 1.11–1.39; WHO obesity aOR 1.26, 95% CI 1.12–1.41). WHO criteria identified more women as normal weight and obese, and less as overweight compared with ethnic-specific criteria. These overall numbers under-represent the total number of women changing BMI group between classifications, as classification change occurs in both directions depending on ethnicity (see section 11.3.2 below for a further breakdown of ethnic-specific BMI versus WHO BMI classifications).

As mentioned in Chapter 7, by identifying risk factors for SGAcust we aim to allow the clinician to better identify women at greater risk, and so institute appropriate SGA surveillance. In obese women, the diagnosis of SGA is made more difficult by body habitus, and so consideration of serial ultrasound scanning in pregnancy is warranted. In addition, we identified a significant increase in risk of SGA among women who have what are generally considered milder complications of pregnancy i.e. gestational hypertension and APH of unknown origin. These women constituted 3.7% and 4.1% of our population respectively, and had an increased odds of SGA of 46% (aOR 1.46, 95% CI 1.21–1.75) and 71% (aOR 1.71, 95% CI 1.45–2.00) respectively. These women should also be considered for fetal growth surveillance by ultrasound. The routine use of antenatal growth charts has been found to identify only 50% of SGA infants (Gardosi & Francis, 1999; Roex et al., 2012), and as 85% of our SGA infants were delivered at term (>37 weeks of gestation) increased antenatal surveillance of women with established risk factors should be continued until delivery. Earlier detection of SGA may lead to more iatrogenic preterm deliveries, but overall if accompanied by careful surveillance should be associated with decreased perinatal morbidity and mortality (Lindqvist & Molin, 2005).

11.3. Pre-eclampsia

The contributions of obesity and ethnicity as risk factors for pre-eclampsia were investigated in Chapter 8 and Chapter 9. In Chapter 8 it was observed that contrary to commonly held perceptions, obese women were just as likely as normal weight women to have preterm pre-eclampsia with associated features of abnormal uterine artery Doppler studies, SGA and multi-system complications of pre-eclampsia. In Chapter 9, also contrary to our hypothesis, it was observed that ethnicity was independently associated with risk of pre-eclampsia with a lower risk among women of Chinese ethnicity and a higher risk among women of Māori ethnicity

compared with European women. (Pacific women had an increased risk of pre-eclampsia that was of borderline significance.)

11.3.1. Obesity and the phenotype of pre-eclampsia

Obesity has a well-established dose dependent association with pre-eclampsia, however the type of pre-eclampsia is poorly characterised. Given the clear similarities between the pathophysiologic features of obesity and the maternal response to pregnancy seen in pre-eclampsia, it has been suggested that obese women are more likely to develop the milder late-onset form of pre-eclampsia (Mbah et al., 2010). Investigation of the phenotypic differences between pre-eclampsia among normal weight women and overweight or obese women will therefore help in the understanding of the pathophysiology of pre-eclampsia in obese women, and may also help to unravel the overall pathophysiology of this complex syndrome.

Although this study was a secondary analysis of the prospectively collected data from the SCOPE study, we had sufficient power to draw conclusions and robust data collection of the clinical variables required for this analysis. The prospective nature of the study also meant we were able to include analysis of uterine artery Doppler studies at 20 weeks of gestation for all but five women with pre-eclampsia (97%), as an early surrogate marker of utero-placental perfusion.

Our finding of no difference in pre-eclampsia phenotype between normal weight and overweight or obese nulliparous women initially seems in conflict with the findings of Mbah and colleagues (Mbah et al., 2010). In a general obstetric population, they documented a sequential increase in late-onset pre-eclampsia (≥34 weeks of gestation) with increasing BMI, Figure 11.1. This was accompanied by a higher aOR for late-onset pre-eclampsia than early-onset pre-eclampsia compared with normal weight women, e.g. super-obese women (BMI ≥ 50 kg/m^2) and early-onset pre-eclampsia aOR 2.97, 95% CI 2.07–4.26, late-onset pre-eclampsia aOR 4.79, 95% CI 4.26–5.39. However using these same data and consistent with our findings, analyses that include only women with pre-eclampsia showed no differences in proportions of early-onset and late-onset pre-eclampsia between BMI categories, e.g. both normal weight and super-obese women with pre-eclampsia have similar rates of early-onset (3.0%) and late-onset (97.0%) disease (Mbah et al., 2010).

In our study we performed multiple analyses of phenotypic characteristics of pre-eclampsia, none of which demonstrated differences between BMI groups. This suggests not only that clinicians should be just as vigilant for development of preterm pre-eclampsia (and associated morbidity) among obese nulliparous women compared with normal weight women, but also that the pathophysiology of the increased rates of pre-eclampsia among obese women includes a component of abnormal placentation. With rising obesity prevalence among obstetric populations internationally, the clinical implication of this finding is both that overall numbers

of women with term and preterm pre-eclampsia will increase and that healthcare resources will be further consumed caring for obese women with potentially serious pregnancy complications.

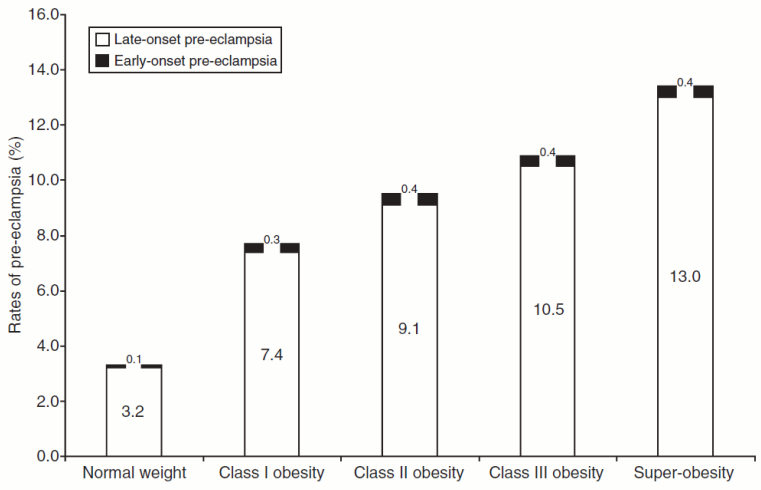


Figure 11.1. Incidence of pre-eclampsia by obesity subtype. Reproduced from Mbah et al., BJOG (2010), Super-obesity and risk for early and late pre-eclampsia, 117 (8) 997-1004. DOI: 10.1111/j.1471-0528.2010.02593.x with permission.

This study was performed prior to updating the NZ customised birthweight model. As the previous model was also used when developing the SCOPE study in 2007, it remains appropriate to use the previous customised birthweight model for this data. If this study was replicated using the new NZ customised birthweight model, it is unlikely to influence the results or conclusions of these analyses as (1) less than 2.5% of infants will change classification from the old to new model i.e. no more than four infants of n = 177 would change classification, and (2) changing SGA birthweight classifications will not influence the other phenotypic characteristics between BMI groups such as gestation at onset of pre-eclampsia, uterine artery Doppler studies etc.

It is important to note that this study was performed on a cohort of nulliparous women without major risk factors for the pregnancy complications of interest to the SCOPE study (pre-eclampsia, SGA and preterm birth). Although this cohort had a large proportion of overweight and obese women (45%) it consisted of predominantly European women (85%) which did not reflect the underlying obstetric population at the time. As a consequence the results of these analyses may not be applicable to a general obstetric population however they provide an important insight into the pathophysiology of obesity-related pre-eclampsia to inform clinicians and future researchers.

11.3.2. Ethnicity and risk of pre-eclampsia

Despite the well-recognised increase in risk of pre-eclampsia among obese women, and substantial differences in rates of obesity between ethnicities, BMI is rarely included in studies investigating risk of pre-eclampsia between ethnic groups. In Chapter 9, we investigated the

independent effect of ethnicity on risk of pre-eclampsia among a general obstetric population, including adjustment for BMI. Contrary to our hypothesis, we found that even after adjusting for clinical confounding, pre-eclampsia rates differed by ethnicity (an increased risk of pre-eclampsia among Māori women, a borderline increased risk among Pacific and Indian women and a decreased risk among Chinese women compared with European). Previous international studies have also found differences in rates of pre-eclampsia between ethnicities, but rarely have these studies included BMI data (Caughey et al., 2005; Irwin et al., 1994; Rao, Cheng, et al., 2006; Rao, Daniels, et al., 2006; Tanaka et al., 2007). Of those that included adjustment for BMI, lower rates of pre-eclampsia are observed among Chinese women (Leung et al., 2008), and higher rates of pre-eclampsia are observed among Hispanic and African American women compared with European women (Myatt et al., 2012). Our study provides the first comprehensive assessment of risk for pre-eclampsia among NZ ethnicities.

It is unclear why women of different ethnicities would have differences in risk for pre-eclampsia, but the most likely explanation for our findings is the inability of the model to account for unknown confounders of ethnicity and pre-eclampsia, possibly a cultural or lifestyle confounder e.g. diet or exercise. The retrospective database nature of this study meant that some factors that other investigators have found to be associated with pre-eclampsia were not able to be included, e.g. high GWG, past or family history of pre-eclampsia or cardiovascular disease etc. However, the clinical confounders that were included in our study are very similar to those used in other analyses, but also include BMI data which as mentioned many other studies are lacking.

Other explanations of true differences in pre-eclampsia risk between ethnicity may relate to metabolic differences between ethnic groups. For example, Māori adults have been observed to have reduced adiponectin levels for the same BMI as European adults (Shand, Elder, Scott, Poa, & Frampton, 2007). This finding, along with the observation that low adiponectin in the first trimester is a risk for pre-eclampsia (D'Anna et al., 2006), suggests one possible mechanism for differences in pre-eclampsia risk. Additionally, high uric acid levels have long been observed among Māori and Pacific peoples along with an associated increased risk of gout (caused by hyperuricaemia) (Hollis-Moffatt et al., 2009). Uric acid has more recently been associated with increased endothelial dysfunction and metabolic syndrome, and is elevated among women with pre-eclampsia (Kharb & Singh, 2001; Rajasingam et al., 2009). Māori and Pacific women have elevated levels of uric acid in pregnancy compared with European women (Barry, Royle, & Lake, 1992), however this analysis was not adjusted for BMI. It is possible that other metabolic differences that may impact on risk of pre-eclampsia exist between ethnicities; however, NZ studies rarely adjust for BMI. Internationally, increased rates of hypertensive disease, metabolic syndrome, cardiovascular disease and diabetes occur in Asian, Indian and African populations compared with European (Colin Bell et al., 2002; Davis, 2008; Palaniappan et al., 2011), which

may relate to a tendency to increased visceral adiposity with subsequent metabolic stressors in these populations (McKeigue et al., 1991; Wang et al., 1994; WHO/IASO/IOTF, 2000).

As expected, increasing BMI was associated with an increasing risk of pre-eclampsia, with obese women having a 2.5-fold increase in odds compared with normal weight women (aOR 2.56, 95% CI 2.11–3.09). For completeness, we also elected to repeat our analyses using WHO BMI criteria for all women. Figure 9.2 illustrates the differences in classifications between ethnic-specific and WHO BMI criteria, with ethnic-specific BMI classifying increased numbers of Māori and Pacific women as normal weight and overweight, and increased numbers of Asian and Indian women as overweight and obese. The greatest change between ethnic-specific and WHO classifications occurred in Indian women, with 30% of women reclassified; WHO BMI (compared with ethnic-specific BMI) resulted in 18% (*n* = 331) of Indian women reclassified as normal weight from overweight, and 12% (*n* = 233) reclassified as overweight from obese. Change of BMI classification also occurred in 15% (*n* = 293) of Māori, 15% (*n* = 564) of Pacific, 18% (*n* = 580) of Chinese and 25% (*n* = 421) of Other Asian women. The use of WHO BMI criteria resulted in a change in statistical significance for odds of pre-eclampsia among Indian women: ethnic-specific BMI, aOR 1.20, 95% CI 0.92-1.56; WHO BMI, aOR 1.41, 95% CI 1.08-1.83. We speculate that the use of WHO BMI criteria in our model over-estimates the risk of pre-eclampsia among Indian women as it underestimates adiposity-related risk. However, even using ethnic-specific BMI the aOR point estimate for Indian ethnicity is raised (aOR 1.20) meaning a true independent increase in risk among Indian women is also possible.

Other independent risk factors for pre-eclampsia in our analysis are consistent with previous reports and include older maternal age (>40 years compared with 20-29 years), nulliparity, hypertensive disease and diabetes. The increased risk observed among type 1 diabetics needs to be interpreted with caution as numbers were small (*n* = 125) and the increased risk among women with unknown diabetes status probably reflects a general increase in risk due to confounders of this variable such as poor antenatal attendance or late booking etc. Although social deprivation on univariable analysis was associated with pre-eclampsia, it was not found to be an independent risk factor in our cohort.

Our finding of a 50% increase in odds of pre-eclampsia among Māori women (aOR 1.51, 95% CI 1.16–1.96) is a further example of health disparities between Māori and European ethnicities. The underlying reason for this disparity is unclear, and further prospective research may assist in understanding this further. Additional research should also focus on the reasons for reduced rates of pre-eclampsia among Chinese women, which may also lead to further understanding of the pathophysiology of pre-eclampsia.

11.4. Ethnicity and Caesarean Section

The contribution of obesity to CS is well established however as ethnicity-related risk of CS is usually investigated using retrospective regional or national datasets, clinical confounders, including BMI, are rarely incorporated into analyses. In Chapter 10 the independent association between ethnicity and both elective and emergency CS is explored, with findings of a reduced rates of elective CS among women of Pacific and Chinese ethnicity, and an increased rate of emergency CS among women of Indian, 'Other Asian' and 'Other' ethnicities compared with European women.

Despite well-established differences in demographics and risk factors between elective and emergency CS (Roman et al., 2008), analyses of risk factors for CS commonly investigate overall CS rates (Barau et al., 2006; Bragg et al., 2010), or perform multinomial analysis of elective and emergency CS where women with elective CS are in the referent group for emergency CS and *vice versa* (Chung et al., 2006). The nulliparous women in our study who underwent elective CS were more likely to be European, older, of higher socioeconomic status and cared for by a private obstetrician (Table 10.2). If these women were included in the comparison group for emergency CS analyses (along with women who had a vaginal birth), this would have biased our results. Therefore, women who had an elective CS were excluded from further emergency CS analysis (n = 923, 7.8% of the initial cohort).

Reasons for reduced rates of elective CS among Pacific and Chinese women (and a trend among Māori women) are unclear, but as confounding factors including socioeconomic status have been accounted for, this may represent patient choice for a midwifery model of obstetric care and vaginal birth. As discussed however, this may also represent a lack of choice available to these women, who may be less likely to be offered or to be able to afford private obstetric care with a consequent reduced access to elective CS. A large multivariable study of CS risk factors in the UK (that analysed elective and emergency CS separately but was not able to account for BMI) also found the highest rates of pre-labour CS were among women of European ethnicity, with most other ethnicities (African, Caribbean, Indian, Bangladeshi, Pakistani, Chinese, Other Asian and Other) having lower adjusted odds (Paranjothy, Frost, & Thomas, 2005). This study also showed higher rates of emergency CS among these same ethnicities (except Chinese), and the authors commented that 'women from ethnic minorities may not be accessing antenatal care', raising the possibility that 'those with problems in their pregnancy that may require delivery by CS, present later, possibly after the onset of labour' (Paranjothy et al., 2005). Our study results were slightly different in that those ethnic groups who had a lower rate of elective CS were not the same as those who had an increase in rate of emergency CS. However the same issue of access to antenatal care may be present, particularly among Pacific women (P. Low et al., 2005), which may partially explain the high rate of public LMC care at birth (63%, n = 735, where public LMC

care is the default care model if a woman does not choose an LMC) and low elective CS rate in these women. In contrast, the majority of Chinese women are under independent midwifery LMC care (71%, *n* = 1235) meaning a lack of choice in caregiver is less likely and low elective CS rates among these women is more likely related to patient (or caregiver) choice.

An increased rate of emergency CS among Indian, Other Asian and Other ethnic groups was also observed. In our study, women of Other Asian ethnicity were a group of women from Southeast Asia (23%, *n* = 196; Thailand, Burma, Indonesia, the Philippines etc.) and a heterogenous group of women from other Asian countries (77%, *n* = 645) including South Asia (Bangladesh, Pakistan, Sri Lanka etc. excluding India) and Korea, Japan etc. (see Appendix 1). As we accounted for comprehensive known confounding factors in our study, it is unclear why emergency CS rates would be elevated among these women, but it is possible there are other clinical factors not able to be accounted for in our study that explain this finding. Alternatively this association may be evidence of over-intervention among these women in our cohort. Reports from international multiethnic populations consistently show higher rates of emergency CS among women of African ethnicity however data for women of South Asian descent are inconsistent (Ibison, 2005; Paranjothy et al., 2005; Thomas et al., 2001). Again, few studies account for BMI, and other methodological limitations restrict the interpretation of these findings.

As expected, increasing BMI was independently associated with an increasing risk of emergency CS however BMI was not associated with elective CS. This lack of association of BMI with elective CS suggests adiposity is not a crucial or deciding factor in the maternal or clinician decision for elective CS. The data handing of BMI in this CS study model differed from our other models in that we elected to include BMI as a continuous rather than a categorical value. Although we believe that ethnic-specific BMI categories better reflect adiposity among a multiethnic population than WHO BMI categories, the categorisation of a continuous variable like BMI also leads to a slight loss of statistical power. As (1) there were no substantial changes in statistical significance between ethnic-specific and WHO BMI categories in the previous SGA and pre-eclampsia analyses, (2) the hypothesis for this study related to ethnicity-associated risk and (3) BMI has a well-established linear relationship with risk of CS; we chose to use BMI as a continuous variable to ensure our model resulted in the best possible estimate for ethnicity associated CS rates.

Our study population of term deliveries to nulliparous women was chosen as we felt this population would best allow us to investigate ethnic differences in mode of delivery. Delivery decisions for parous women are strongly influenced by the mode of delivery of previous babies, with previous CS a substantial risk factor for repeat (particularly elective) CS (MacDorman et al., 2008; Stavrou et al., 2011; Thomas et al., 2001). This association between previous CS and CS in a subsequent pregnancy also means that prevention of a CS in a first birth substantially reduces

a woman's risk of CS in future pregnancies. Reducing CS rates among nulliparous women has the potential to substantially reduce overall CS rates (MacDorman et al., 2008).

We also excluded preterm birth as it is an inherently pathological process and women do not usually have a choice of elective CS when faced with this situation. Emergency CS with preterm births are more likely to occur due to fetal concerns but are unlikely to differ by ethnicity. For completeness we performed a sub-analysis of emergency CS for preterm births alone, and no independent ethnicity effect on emergency CS was observed (multivariable *P* value for ethnicity = 0.07). Placenta praevia was excluded as it is a contraindication to vaginal birth, and we also excluded stillbirth and major congenital abnormalities as the presence of these fetal pathologies are likely to have an influence on decision-making at the time of birth. After adjustment for known clinical risk factors for CS we believe we have adjusted for the majority of clinical determinants of elective and emergency CS meaning the differences in CS rates between ethnicities are likely to be related to non-clinical factors.

In NZ, there have been two studies that have investigated CS risk by ethnicity and found lower rates of elective CS among Māori and Pacific women compared with Other women (Harris et al., 2007; Sadler et al., 2002) with one of these studies also describing lower rates of emergency CS among Māori women (Harris et al., 2007). These studies had data limitations, particularly lack of BMI data and the use of a heterogeneous group of 'Other' women as the reference group. Additionally Harris and colleagues were unable to accurately adjust for parity and used multinomial analyses of elective and emergency CS (Harris et al., 2007). However, our finding of a lower elective CS rates among Pacific women (and a trend to a decreased rate among Māori women) is consistent with these reports. Also consistent with Sadler and colleagues (and in contrast to Harris and colleagues), we observed no difference in emergency CS rates among Māori and Pacific women. As Māori and Pacific women have in general higher risk pregnancies, it has been suggested that decreased intervention rates (including CS) among these women may reflect inequalities in care (Harris et al., 2007). However in our term, nulliparous cohort, as we have already adjusted for known confounding factors, it can be argued that rather than Pacific and Māori rates of elective CS being too low, rates among European women may be too high. This argument is supported by our finding that elective CS are more likely among affluent women under private obstetric care, and suggests that these elective CS may be related to patient request or other non-clinical factors. The observation of no differences in rates of emergency CS between Māori and Pacific compared with European women is reassuring, as it suggests no difference in access to emergency CS between these groups. Even with poorer perinatal outcome among Māori and Pacific women, as we have adjusted for confounding we would not expect these women to have differences in emergency CS rates unless there were

ethnic inequities in healthcare. Importantly, we also have no evidence of over-intervention among Māori and Pacific women compared with European women.

As this study was performed in a nulliparous cohort of women, the ethnicity associations we have observed may not persist when examining a full general obstetric cohort. In addition, as this study was performed in a single centre, there is the possibility that differences in practice exist in other centres (including ethnic discrimination such as unconscious bias, cultural misunderstandings, or uninformed beliefs (Human Rights Commission, 2012)); however, as we have accounted for the major clinical confounders of elective and emergency CS the findings of this study should be applicable to other NZ centres. These findings however are not necessarily applicable to birth cohorts outside of NZ, as maternity systems and delivery of care in pregnancy differ. Although our data were prospectively recorded, this was a retrospective analysis. A limitation of this study is that we did not have information on the indication for CS, which makes it more difficult to assess the appropriateness of the decision for CS. These data may also have provided additional information as to why women of Indian, Other Asian and Other ethnicities had higher rates of emergency CS.

Our findings suggest that in our cohort of nulliparous term births, elective CS among European nulliparous women and emergency CS among Indian, Other Asian and Other women may be too high, or else other as-yet unknown clinical factors may explain these differences.

11.5. Future research

The study findings presented above raise interesting avenues for future research. Our observational studies, as always, can identify associations, but causality cannot be attributed. Associations between exposures and outcomes in observational studies can also be over-or under- stated through residual confounding,[6] Apart from the purpose-designed SCOPE data used in the analysis of pre-eclampsia phenotype in Chapter 8, the NWH data was routine maternity data (albeit prospectively collected and routinely cleaned and monitored) meaning some variables of interest were not collected and so cannot be included in analyses. Our findings of ethnic differences in rates of pre-eclampsia and CS should be confirmed in prospective studies that are also able to include detailed information on cultural and/ or lifestyle factors that may influence results, as well as (in the case of CS) detailed delivery information including indication for CS. Of particular interest is the finding of lower rates of pre-eclampsia among Chinese women. Exploration of this finding may help in the understanding of the pathophysiology of pre-eclampsia.

[6] Residual confounding occurs when (1) a confounding variable does not fully account for the effect of that variable on the outcome of interest (either through an imperfect variable or poor quality data), or (2) additional confounding exists from unknown variables.

As has already been mentioned, the majority of infants included in the analyses of perinatal death among SGA infants (Chapter 6) and risk factors for SGAcust infants (Chapter 7) were also used in the creation of the coefficients for the new customised birthweight model (Chapter 6). A lack of independence between these study populations may mean some associations are over- or under-represented, however we did not have access to a further large independent cohort. The analyses of SGA-related perinatal death in Chapter 6 and SGAcust risk factors in Chapter 7 should be reproduced in a large independent study cohort.

Through the investigation of the relationship between ethnic-specific and WHO BMI classifications on various pregnancy outcomes, we had hoped to be able to comment on the appropriateness of the use of ethnic-specific BMI categories in pregnancy. However our analyses revealed only small differences in ethnicity-related risk between the two criteria, with few changes in statistical significance. Although ethnic-specific BMI criteria seem sensible based on literature on Asian and Indian non-pregnant populations, and one study among Hong Kong Chinese pregnant women (Leung et al., 2008), there are no data to guide the use of ethnic-specific BMI criteria among Māori and Pacific adults, let alone in pregnancy, and this dataset was too small to clarify this. As Māori and Pacific women have higher risk pregnancies overall, it may not be appropriate to 'reduce' their adiposity-related risk by raising BMI criteria for overweight and obesity in these women based only on differences in fat mass percentage. In our studies, pregnancy outcomes were similar between classifications, but we do not as-yet have enough information to recommend routine use of ethnic-specific BMI in pregnancy. Further investigation of the appropriateness of ethnic-specific BMI in pregnancy would require a large multi-ethnic cohort, with sufficient numbers that multivariable analysis can be performed for low prevalence pregnancy outcomes (e.g. pre-eclampsia approximately 3%) within small BMI groups (e.g. increments of 2-3kg/m^2), similar to the methodology of Leung and colleagues (Leung et al., 2008), or to create multivariable models of predicted disease prevalence by continuous BMI compared between ethnic groups, similar to the methodology of Chiu and colleagues (Chiu et al., 2011).

Another important pregnancy outcome that is related to both obesity and ethnicity is GDM. Although in NZ universal screening for GDM is recommended (as risk factor screening for GDM has poor sensitivity and specificity), this does not always occur due to late booking, poor antenatal attendance etc. Additionally, in previous years although women with diagnosed GDM were accurately recorded in the NWH clinical database (they were followed through a specialist clinic), this database did not reliably collect GDM screening data. As a result approximately one third of women had unknown diabetes status in the 2006 to 2009 data that was used for the majority of analyses above. Unknown status meant a woman was either screen negative and this was not recorded, or no screening test was performed. This data deficiency has been identified

and addressed with the anticipated result of less missing data in the future. As with type-2 diabetes, there are perceptions that some ethnic groups are overrepresented in their prevalence of GDM at lower BMIs (Chiu et al., 2011; Leung et al., 2008; WHO/IASO/IOTF, 2000), and formal multivariable analysis should be performed to investigate this.

Chapter 8 investigated the differences in clinical phenotype of pre-eclampsia between normal weight women and overweight or obese women and found no differences. This suggests similarities in the underlying pathophysiology of pre-eclampsia between BMI groups; however, despite the clinical phenotype of pre-eclampsia being unchanged by BMI, other predisposing factors such as lipids, inflammatory and oxidative stress markers etc. are likely to differ by BMI in women with pre-eclampsia. Further research into the differences and similarities of pre-eclampsia between different BMI categories may not only determine why obesity is a risk factor for pre-eclampsia, but also why some obese women get pre-eclampsia while others do not. Better understanding of the pathophysiology of pre-eclampsia in obese women is particularly important in the current era of escalating obesity prevalence.

11.6. Summary and Conclusions

The above thesis has contributed to more detailed understanding of the impacts of both obesity and ethnicity on three important adverse pregnancy outcomes; SGA (and birthweight), pre-eclampsia and CS. In summary:

- maternal characteristics such as ethnicity and increasing maternal height and weight have physiological influences on normal birthweight that help to better identify SGA infants at-risk of perinatal death
- obesity is independently associated with a 25% increase in odds of SGAcust
- in women with pre-eclampsia overweight and obese women are just as likely to have preterm pre-eclampsia as normal weight women
- compared with European women, Chinese women have a lower risk and Māori women a higher risk of pre-eclampsia (with a borderline increase in risk among Pacific and Indian women)
- among term nulliparous women; compared with European women, Pacific and Chinese women have a lower rate of elective CS and Indian, Other Asian and Other women a higher rate of emergency CS. No differences in emergency CS rates exist between Māori and Pacific women compared with European.

The overall impact of obesity on society is huge and increasing in both NZ and internationally, including in pregnancy. Obesity in pregnancy leads to an intergenerational propagation of metabolic risk and the better we understand these effects, the better we may be prepared to

manage or attempt to mitigate these risks for both mother and infant. Significant discrepancies in pregnancy outcomes have been observed between ethnic groups, and this can be partially explained by differing rates of obesity. However even after accounting for adiposity, differences still exist. Further investigation of cultural and lifestyle factors that may impact on pregnancy outcomes could improve our understanding of why ethnicity has an impact on pregnancy outcomes.

Appendix 1 | Ethnicity data coding and prioritisation

Ethnicity data coding and prioritisation (Ministry of Health, 2004a)

In the NZ health and disability sector, an individual may choose up to three ethnicities in a standardised question, Figure 1. The below tables are the codesets for coding and prioritising these self-reported ethnicities (levels 1 and 2 plus reference groups for level 2) for statistical reporting to the Ministry of Health, NZ.

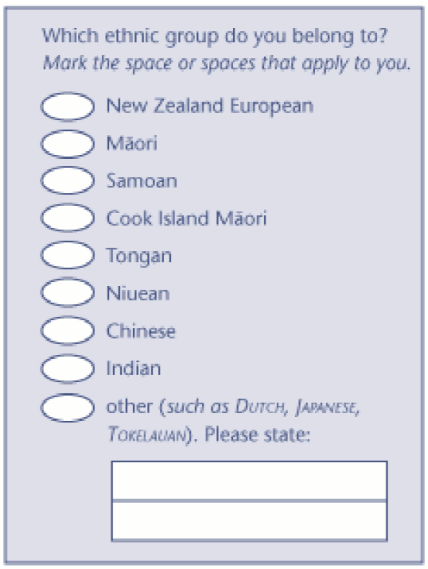


Figure 1. Standard ethnicity collection question (Ministry of Health, 2004)

Coding Levels

NFD = not further defined NEC = not elsewhere classified

Level 1		
Priority order	**Ethnic group code**	**Ethnic group description**
1	2	Māori
2	3	Pacific Peoples
3	4	Asian
4	5	Middle Eastern/Latin American/African
5	6	Other Ethnicity
6	9	Residual Categories
7	1	European

Level 2		
Priority order	**Ethnic group code**	**Ethnic group code description**
1	21	Māori
2	35	Tokelauan
3	36	Fijian
4	34	Niuean
5	33	Tongan
6	32	Cook Island Maori
7	31	Samoan
8	37	Other Pacific Island
9	30	Pacific Island NFD*
10	41	South East Asian
11	43	Indian
12	42	Chinese
13	44	Other Asian
14	40	Asian NFD
15	52	Latin American / Hispanic
16	53	African
17	51	Middle Eastern
18	54	Other
19	12	Other European
20	10	European NFD
21	11	NZ European

Level 2 reference groups				
Code	**Health Care User Ethnicity Response:**			
10 - European NFD	• European			
11 - NZ European	• NZ European • New Zealander			
12 - Other European	• Afrikaner • Albanian • American (US) • Armenian • Australian • Austrian • Belgian • Belorussian • Bosnian	• Cypriot • Czech • Dalmatian • Danish • Dutch/ Netherlands • English • Estonian • European – NEC	• Hungarian • Icelander • Irish • Italian • Latvian • Lithuanian • Macedonian • Maltese • Manx	• Russian • Sardinian • Scottish/ Scots • Serb/ Serbian • Shetland Islander • Slavik/Slav • Slovak • Slovene/

Level 2 reference groups				
Code	**Health Care User Ethnicity Response:**			
	• British – NEC + NFD • Bulgarian • Burgher • Canadian • Celtic • Channel Islander • Cornish • Corsican • Croat/Croatian	• + NFD • Falkland Islander/Kelper • Finnish • Flemish • French • Gaelic • German • Greek (inc Greek Cypriot) • Greenlander	• New Caledonian • Norwegian • Orkney Islander • Polish • Portuguese • Romanian/Rumanian • Romany/Gypsy	• Slovenian • South African • South Slav – NEC + NFD • Spanish • Swedish • Swiss • Ukrainian • Welsh • Yugoslavian • Zimbabwean
21 - Māori	• Māori			
30 - Pacific Island - NFD	• Pacific Islander			
31 - Samoan	• Samoan			
32 - Cook Island Māori	• Aitutaki Islander • Atiu Islander • Cook Island Māori (NFD)	• Mangaia Islander • Manihiki Islander • Mauke Islander	• Mitiaro Islander • Palmerston Islander • Penrhyn Islander	• Pukapuka Islander • Rakahanga Islander • Rarotongan
33 - Tongan	• Tongan			
34 - Niuean	• Niuean			
35 - Tokelauan	• Tokelauan			
36 - Fijian	• Fijian Except Fijian Indian/ Indo-Fijian			
37 - Other Pacific Peoples	• Admiralty Islander • Austral Islander • Australian Aboriginal • Belau/Palau Islander • Bismark Archipelagoan • Bougainvillean • Caroline Islander • Easter Islander • Gambier Islander • Guadalcanalian	• Guam Islander/ Chamorro • Hawaiian • I-Kiribati/ Gilbertese • Kanaka/Kanak • Malaitian • Manus Islander • Marianas Islander • Marquesas Islander • Marshall Islander • Nauru Islander • New Britain Islander	• New Georgian New Irelander • Ocean Islander/ • Banaban • Papuan/New Guinean • Phoenix Islander • Pitcairn Islander • Rotuman Islander • Santa Cruz Islander • Society Islander (incl Tahitian) • Solomon Islander	• Thursday Islander • Torres Strait Islander • Tuamotu Islander • Tuvalu Islander/Ellice Islander • Vanuatu Islander/ New Hebridean • Wake Islander • Wallis Islander • Yap Islander
40 – Asian NFD				

Level 2 reference groups				
Code	**Health Care User Ethnicity Response:**			
41 - Southeast Asian	• Burmese • Cambodian • Filipino	• Indonesian/ Javanese • Kampuchean/ Khmer • Lao/Laotian	• Malay/Malayan • South East Asian – NEC + NFD • Sundanese/ Sumatran	• Thai/Tai/ Siamese • Vietnamese
42 - Chinese	• Chinese – NEC + NFD • Hong Kong Chinese	• Kampuchean Chinese • Malaysian Chinese	• Singaporean Chinese • Taiwanese Chinese	• Vietnamese Chinese
43 - Indian	• Anglo Indian • Bengali	• Fijian Indian • Gujarati	• Indian – NEC + NFD • Punjabi	• Sikh • Tamil
44 - Other Asian	• Afghani • Bangladesh • Eurasiani	• Japanese • Korean • Nepalese	• Other Asian - NEC • Pakistani • Sinhalese	• Tibetan • Sri Lankan • Tamil
51 - Middle Eastern	• Algerian • Arab • Assyrian • Egyptian • Iranian/Persian	• Iraqi • Israeli/Jewish/ Hebrew • Jordanian • Kurd • Lebanese	• Libyan • Middle Eastern- NEC + NFD • Moroccan • Omani • Palestinian	• Syrian • Tunisian • Turkish (inc Turkish Cypriot) • Yemeni
52 - Latin American/ Hispanic	• Argentinian • Bolivian • Brazilian • Chilean • Colombian	• Costa Rican • Creole (Latin America) • Ecuadorian • Guatemalan • Guyanese	• Honduran • Latin American/ Hispanic NEC + NFD • Malvinian • Mexican • Nicaraguan • Panamanian	• Paraguayan • Peruvian • Puerto Rican • Uruguayan • Venezuelan
53 - African	• African American • African – NEC + NFD • Creole (US)	• Eritrean • Ethiopian • Ghanaian	• Jamaican • Kenyan • Nigerian	• Somali • Ugandan • West Indian/ Caribbean
61 - Other	• Central American Indian • Inuit/Eskimo	• Mauritian Islander • North American Indian	• Other – NEC + NFD • Seychelles Islander	• South African Coloured • South American Indian
94 - Don't Know	• Don't Know			
95 - Refused to Answer				
97 - Response unidenti-fiable				
99 - Not Stated				

Appendix 2 | The birthweight customisation procedure

Detailed methods of the birthweight customisation procedure (Gardosi & Francis, 2012c)

A truncated version of GROW documentation follows:

GROW documentation

This document describes the application of the 'customised growth potential' to assess fetal size and growth, using the Gestation Related Optimal Weight (GROW) software.

GROW – Customised Weight Centiles

- to calculate birthweight centiles individually or in bulk;

GROW – Customised Growth Charts

- to plot fundal height and estimated fetal weight

Introduction

The customised growth chart concept was developed initially in Nottingham in the early 1990s (Gardosi et al., 1992). While recognising the importance of growth for fetal well being, we became increasingly aware that existing charts were not useful for clinical assessment in a heterogeneous maternity population.

Over time, we have been able to test the concept of adjustable or customised assessment of growth and birthweight from many different perspectives. We are constantly seeking to improve and add to the database which allows application in different populations.

The project has been fortunate to benefit from a number of dedicated researchers, statisticians and programmers over the years, who are acknowledged in various publications referenced here. While the strengths of the method and its implementation are due to the efforts my collaborators, any weaknesses are entirely my own responsibility.

We hope that you find our software useful for the assessment of fetal growth and birth weight. We are continuing to seek to improve it, and comments and criticisms are always welcome, so please do not hesitate to get in touch!

Professor Jason Gardosi MD FRCOG FRCSED
Director, West Midlands Perinatal Institute,
Birmingham B6 5RQ, United Kingdom
Tel +44 121 687 3400; Fax +44 121 687 3401

e-mail: jason.gardosi@pi.nhs.uk;
websites: www.pi.nhs.uk and www.gestation.net

General Concepts

The software allows the generation of an individual or 'customised' standard by adjusting for physiological factors which are known to affect fetal growth. The pregnancy characteristics are entered to calculate the **Term Optimal Weight (TOW, Section 3)**. This is the weight which the baby is predicted to achieve in the absence of pathological influences. The calculation of TOW is centred on 40.0 weeks (280 days).

Through this point TOW, the proportionality curve is plotted to delineate how this weight is expected to be reached in a normal pregnancy (see section 5). This gives an individually adjusted **Gestation Related Optimal Weight (GROW)** curve. Around this optimal line, the normal variation can be calculated and limits such as the 10th and 90th centile lines drawn. Thus neonatal weights from previous pregnancies, as well as fundal height measurements or fetal weight estimations in the current pregnancy, can be seen in relation to individually adjusted optimal weight limits.

There are 3 underlying **principles for GROW-percentiles**:

1. Weights are assessed in reference to a standard which is **individually adjusted** for physiological pregnancy variables (maternal height, weight, parity and ethnic group); e.g. at 40 weeks, a 3000g baby is small for an average size mother but may be normal for a small mother.
2. The standard is **'optimised' to obtain the growth potential**, i.e. pathological variables such as smoking are excluded. This means that the expected term baby weight for a mother who smokes is calculated as if she was a non-smoker, so that if her baby's growth is affected, it is more likely to be detected.
3. Optimal weight is calculated using a **fetal** rather than a **neonatal** weight standard. Preterm neonatal weights are abnormal by definition, and have often been affected by fetal growth retardation preceding spontaneous or iatrogenic preterm delivery. Eg. at 32 weeks, a 1500g baby would fall within normal birth weight limits, but is small according to a 32 week fetal weight standard derived from normal term pregnancies.

Calculating the Optimal Weight

The main non-pathological factors affecting birth weight are **gestational age, maternal height, maternal weight at booking, parity and ethnic group** (Gardosi et al., 1992) Coefficients to

adjust for these were derived from a dataset of around 40,000 ultrasound dated deliveries. They allow calculation of an expected birth weight for each pregnancy, and the 'customised' percentile which a particular weight has achieved in relation to this expected endpoint. An alternative method to adjust for such variables is to calculate the individual birth weight ratio (IBR) (Gardosi, Mongelli, & Mul, 1995; Sanderson, Wilcox, & Johnson, 1994; Wilcox, Johnson, Maynard, Smith, & Chilvers, 1993) IBR follows principle 1 above, i.e. adjusts for individual variation, but does not optimise (principle 2) or apply a fetal weight standard (principle 3).

Other physiological variables such as **paternal height** have, unless extreme, a relatively minor effect (Wilcox et al., 1995) and may in any case not always be known with certainty. **Maternal age** appears to play no significant role once parity is controlled for.

Pathological factors such as **smoking, social deprivation, pre-eclampsia or diabetes** are also known to be related to birth weight but are not adjusted for. The purpose is to calculate the optimal weight, against which the actual weight can be assessed. Thus 'term optimal weight' (TOW) represents an ideal standard rather than the average for an unselected population. TOW is centred on day 280, the median length of pregnancy in our population.

Coefficients for adjusting the term optimal weight (TOW)

Coefficients are derived from suitable databases using a multiple regression model centred on a standard gestational age (280 days), the largest ethnic group, average maternal height and weight at booking, and first pregnancy (para 0). In addition, gender is listed as an 'average' i.e. sex neutral. The regression model has a constant to which weight is added or subtracted for each of the variables, according to the formula

TOW = constant + htao + wtao + ethao + parao + sexao

where 'ao' are add-ons, respectively, for

ht = maternal height
wt = maternal weight at booking (first visit)
eth = ethnic origin
par = parity and
sex = sex of fetus/neonate, if known

UK coefficients

Originally based on Nottingham database (1987-1991), (Gardosi, Mongelli, Wilcox, et al., 1995) the coefficients have recently been updated using the more recent West Midlands database of 96,830 births, 2009-2011 (Figure 1. submitted).

Name of coefficient	Contribution in grams
Constant	3454.4
Maternal height (*median 163 cm*) deviation	
for each cm	+8.427
Maternal weight (*median 64 kg*) deviation:	
for each kg	+7.619
for each kg^2	-0.113
for each kg^3	+0.001
Ethnic origin (*default European incl British Isles and those of European origin elsewhere. eg Australia, Canada, USA*)	
Indian	-206.4
Pakistani	-156.8
Bangladeshi	-125.7
African Caribbean	-116.0
African (sub-Sahara)	-63.7
Middle East (inc North Africa)	-90.0
Far East Asian (eg China, Japan)	+64.0
South East Asia (eg Thailand, Malaysia, Philippines)	+71.5
Other	-60.0
Parity at beginning of pregnancy (*default para 0*)	
Para 1	+111.0
Para 2	+154.8
Para 3 or more	+151.3
Sex of fetus/neonate (*default 'average' i.e. sex neutral*)	
Male	+52.6
Female	-52.6

Figure 1. UK (Nottingham) coefficients. SE of model = 407.5, giving CV = 0.11797

Proportionality curve

Once the TOW (term optimal weight, predicted for 280 days gestation) is calculated, it is combined with a proportionality growth function to determine the optimal weight at all gestations. This function transforms the average weights at all gestations to a percent of term weight in that population. The proportionality principle can be used retrospectively (birthweight to fetal weight) or to project fetal weight to predict birth weight (Gardosi, Mongelli, Wilcox, et al., 1995; Mongelli & Gardosi, 1996) .

Reviews of published formulae for fetal weight gain suggest that most follow a similar pattern, or growth dynamic, although the endpoints (term weights) may vary (Gardosi, 1994; Gardosi, Mongelli, Wilcox, & Chang, 1994). Our standard formula is derived from Hadlock's fetal weight equation (Hadlock et al., 1991)which closely reflects normal fetal weight in other populations. The proportionality equation is :

$$\% \text{ weight} = 299.1 - 31.85\ GA + 1.094\ GA^2 - 0.01055\ GA^3$$

where GA = gestational age in weeks.

Thus for each individually predicted Term Optimal Weight (TOW), the formula is used to produce a Gestation Related Optimal Weight (GROW).

Normal range

The normal limits of weight for all gestations are calculated from the coefficient of variation (CV) of the TOW. It is derived from the SD and Mean (Constant) of the population through the regression model, and defined as:

$$CV\ (\%) = \frac{SD * 100}{Mean}$$

For the UK database, SD = 389, Constant = 3455. Thus, in this case CV = 11%

The centile limits are derived using Z scores. For example, the 90th and 10th centiles are represented by z = ± 1.28.

Therefore: z * CV = ± 1.28 * 11% = ± 14%;

Thus: 90th centile = TOW + 14%
10th centile = TOW – 14%

E.g. the 10th to 90th centile range for a TOW of 3500g is 3500 ± 14%, i.e. range 3010-3990g.

The effect of using the CV is that the range designated as 'normal' becomes narrower for lower TOWs and wider for higher TOWs. Thus a small baby is allowed a smaller range of normal variation in absolute terms. The method compensates for the positive skewness of the distribution of birth weight.

The proportionality weight equation is fitted through the three term points: TOW, TOW+14% and TOW–14%. This defines the 50th, 90th and 10th centile lines respectively for the gestation period 24 to 42 weeks. This principle is used in the applications described in the following sections.

GROW - Customised Weight Centiles

The GROW Customised Weight Centile module allows a weight-for-gestational age centile to be determined for previous babies, and for estimated fetal weights and birth weight in the current pregnancy.

Centiles for previous pregnancies are calculated for the corresponding parity, i.e. the parity of the mother at the *beginning* of the respective pregnancy. However no adjustment is made for maternal weight if it was different in a previous pregnancy. The application can also be used for a fetal weight centile when the sex of the baby is not known.

Precise gestational age (at birth, or at the point of EFW measurement) needs to be entered.

NB: When a particular data item is missing or unobtainable, e.g. maternal height, partial customisation can be undertaken by entering an estimate or population average - e.g. 165 cm.

The GROW Customised Centile Calculator comes also in spreadsheet format to allow calculation of centiles for whole databases.

List of references

Abate, N., & Chandalia, M. (2003). The impact of ethnicity on type 2 diabetes. *Journal of Diabetes & its Complications, 17*(1), 39-58.

Abrams, B., Carmichael, S., & Selvin, S. (1995). Factors associated with the pattern of maternal weight gain during pregnancy. *Obstetrics & Gynecology, 86*(2), 170-176.

Ahmad, A., & Samuelsen, S. (2012). Hypertensive disorders in pregnancy and fetal death at different gestational lengths: a population study of 2 121 371 pregnancies. *BJOG, 119*(12), 1521-1528.

Albanese, C. V., Diessel, E., & Genant, H. K. (2003). Clinical applications of body composition measurements using DXA. *Journal of Clinical Densitometry, 6*(2), 75-85.

Alberry, M., & Soothill, P. (2007). Management of fetal growth restriction. *Archives of Disease in Childhood Fetal & Neonatal Edition, 92*(1), F62-67.

Alderliesten, M. E., Vrijkotte, T. G. M., Van Der Wal, M. F., & Bonsel, G. J. (2007). Late start of antenatal care among ethnic minorities in a large cohort of pregnant women. *BJOG: An International Journal of Obstetrics & Gynaecology, 114*(10), 1232-1239.

Alexander, G. R., Himes, J. H., Kaufman, R. B., Mor, J., & Kogan, M. (1996). A United States national reference for fetal growth. *Obstetrics & Gynecology, 87*(2), 163-168.

Alexander, G. R., Kogan, M. D., & Himes, J. H. (1999). 1994-1996 U.S. singleton birth weight percentiles for gestational age by race, Hispanic origin, and gender. *Maternal & Child Health Journal, 3*(4), 225-231.

Alexander, G. R., Wingate, M. S., Mor, J., & Boulet, S. (2007). Birth outcomes of Asian-Indian-Americans. *International Journal of Gynaecology & Obstetrics, 97*(3), 215-220.

Alexander, J. M., McIntire, D. D., & Leveno, K. J. (2001). Prolonged pregnancy: induction of labor and cesarean births. *Obstetrics & Gynecology, 97*(6), 911-915.

Alexandra, P., Vassilios, B., Alexandra, V., George, K., Vassiliki, L., & Chryssa, B. (2011). Population-based trends of pregnancy outcome in obese mothers: what has changed over 15 years. *Obesity, 19*(9), 1861-1865.

Alfirevic, Z., Devane, D., & Gyte, G. M. L. (2006). Continuous cardiotocography (CTG) as a form of electronic fetal monitoring (EFM) for fetal assessment during labour. *Cochrane Database of Systematic Reviews, 3*, CD006066.

Allen, V. M., Joseph, K., Murphy, K. E., Magee, L. A., & Ohlsson, A. (2004). The effect of hypertensive disorders in pregnancy on small for gestational age and stillbirth: a population based study. *BMC Pregnancy Childbirth, 4*(1), 17.

Althabe, F., Sosa, C., Belizan, J. M., Gibbons, L., Jacquerioz, F., & Bergel, E. (2006). Cesarean section rates and maternal and neonatal mortality in low-, medium-, and high-income countries: an ecological study. *Birth, 33*(4), 270-277.

Alves, B., & Sheikh, A. (2005). Investigating the relationship between affluence and elective caesarean sections. *BJOG: An International Journal of Obstetrics & Gynaecology, 112*(7), 994-996.

Ananth, C. V., Berkowitz, G. S., Savitz, D. A., & Lapinski, R. H. (1999). Placental abruption and adverse perinatal outcomes. *JAMA, 282*(17), 1646-1651.

Ananth, C. V., Demissie, K., Smulian, J. C., & Vintzileos, A. M. (2001). Relationship among placenta previa, fetal growth restriction, and preterm delivery: a population-based study. *Obstetrics & Gynecology, 98*(2), 299-306.

Andersson, L., Sundstrom-Poromaa, I., Wulff, M., Astrom, M., & Bixo, M. (2004). Neonatal outcome following maternal antenatal depression and anxiety: a population-based study. *American Journal of Epidemiology, 159*(9), 872-881.

Aron, D. C., Gordon, H. S., DiGiuseppe, D. L., Harper, D. L., & Rosenthal, G. E. (2000). Variations in risk-adjusted cesarean delivery rates according to race and health insurance. *Medical Care, 38*(1), 35-44.

Asarian, L., & Geary, N. (2006). Modulation of appetite by gonadal steroid hormones. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences, 361*(1471), 1251-1263.

Ashmead, G. G. (2003). Smoking and pregnancy. *Journal of Maternal-Fetal & Neonatal Medicine, 14*(5), 297-304.

Askelund, K. J., & Chamley, L. W. (2011). Trophoblast deportation part I: review of the evidence demonstrating trophoblast shedding and deportation during human pregnancy. *Placenta, 32*(10), 716-723.

Atkinson, R. L., Pietrobelli, A., Uauy, R., & Macdonald, I. A. (2012). Are we attacking the wrong targets in the fight against obesity?: the importance of intervention in women of childbearing age. *International Journal of Obesity, 36*(10), 1259-1260.

Atlantis, E., Goldney, R. D., & Wittert, G. A. (2009). Obesity and depression or anxiety. *BMJ, 339*, b3868.

Augustine, R. A., Ladyman, S. R., & Grattan, D. R. (2008). From feeding one to feeding many: hormone-induced changes in bodyweight homeostasis during pregnancy. *Journal of Physiology, 586*(2), 387-397.

Australasian Society for Ultrasound in Medicine. (2001-2007a). Guidelines for the mid trimester obstetric scan *Policies and Statements D2*. http://www.asum.com.au/site/policies.php: ASUM.

Australasian Society for Ultrasound in Medicine. (2001-2007b). Statement on normal ultrasonic fetal measurements *Policies and Statements D7*. http://www.asum.com.au/site/policies.php: ASUM.

Bada, H. S., Das, A., Bauer, C. R., Shankaran, S., Lester, B. M., Gard, C. C., . . . Higgins, R. (2005). Low birth weight and preterm births: etiologic fraction attributable to prenatal drug exposure. *Journal of Perinatology, 25*(10), 631-637.

Bai, J., Wong, F. W., Bauman, A., & Mohsin, M. (2002). Parity and pregnancy outcomes. *American Journal of Obstetrics & Gynecology, 186*(2), 274-278.

Bailit, J. L. (2005). Hyperemesis gravidarium: Epidemiologic findings from a large cohort. *American Journal of Obstetrics & Gynecology, 193*(3 Pt 1), 811-814.

Bakewell, J. M., Stockbauer, J. W., & Schramm, W. F. (1997). Factors associated with repetition of low birthweight: Missouri longitudinal study. *Paediatric and Perinatal Epidemiology, 11 Suppl 1*, 119-129.

Barau, G., Robillard, P. Y., Hulsey, T. C., Dedecker, F., Laffite, A., Gerardin, P., & Kauffmann, E. (2006). Linear association between maternal pre-pregnancy body mass index and risk of caesarean section in term deliveries. *BJOG, 113*(10), 1173-1177.

Barker, D. J. (1995). Fetal origins of coronary heart disease. *BMJ, 311*(6998), 171-174.

Barker, D. J. (2004). The developmental origins of adult disease. *Journal of the American College of Nutrition, 23*(6 Suppl), 588S-595S.

Barker, D. J., Winter, P. D., Osmond, C., Margetts, B., & Simmonds, S. J. (1989). Weight in infancy and death from ischaemic heart disease. *Lancet, 2*(8663), 577-580.

Barley, K., Aylin, P., Bottle, A., & Jarman, B. (2004). Social class and elective caesareans in the English NHS. *BMJ, 328*(7453), 1399.

Barry, C. L., Royle, G. A., & Lake, Y. (1992). Racial variation in serum uric acid concentration in pregnancy: a comparison between European, New Zealand Maori and Polynesian women. *Australian & New Zealand Journal of Obstetrics & Gynaecology, 32*(1), 17-19.

Baschat, A. A. (2003). Integrated fetal testing in growth restriction: combining multivessel Doppler and biophysical parameters. *Ultrasound in Obstetrics & Gynecology, 21*(1), 1-8.

Basso, O., & Baird, D. D. (2003). Infertility and preterm delivery, birthweight, and Caesarean section: a study within the Danish National Birth Cohort. *Human Reproduction, 18*(11), 2478-2484.

Basso, O., Olsen, J., & Christensen, K. (1998). Risk of preterm delivery, low birthweight and growth retardation following spontaneous abortion: a registry-based study in Denmark. *Int J Epidemiol, 27*(4), 642-646.

Battin, M. R., McCowan, L. M., George-Haddad, M., & Thompson, J. M. (2007). Fetal growth restriction and other factors associated with neonatal death in New Zealand. *Australian & New Zealand Journal of Obstetrics & Gynaecology, 47*(6), 457-463.

Bdolah, Y., Sukhatme, V. P., & Karumanchi, S. A. (2004). Angiogenic imbalance in the pathophysiology of preeclampsia: newer insights. *Seminars in Nephrology, 24*(6), 548-556.

Bech, B. H., Obel, C., Henriksen, T. B., & Olsen, J. (2007). Effect of reducing caffeine intake on birth weight and length of gestation: randomised controlled trial. *BMJ, 334*(7590), 409.

Beeby, P. J., Bhutap, T., & Taylor, L. K. (1996). New South Wales population-based birthweight percentile charts. *Journal of Paediatrics & Child Health, 32*(6), 512-518.

Belizan, J. M., Althabe, F., & Cafferata, M. L. (2007). Health consequences of the increasing caesarean section rates. *Epidemiology, 18*(4), 485-486.

Bell, C., Swinburn, B. A., Stewart, A., Jackson, R., Tukuitonga, C., & Tipene-Leach, D. (1996). Ethnic differences and recent trends in coronary heart disease incidence in New Zealand. *New Zealand Medical Journal, 109*(1017), 66-68.

Berthoud, H. R. (2006). Homeostatic and non-homeostatic pathways involved in the control of food intake and energy balance. *Obesity, 14 Suppl 5*, 197S-200S.

Betran, A. P., Gulmezoglu, A. M., Robson, M., Merialdi, M., Souza, J. P., Wojdyla, D.. . . Bataglia, V. (2009). WHO global survey on maternal and perinatal health in Latin America: classifying caesarean sections. *Reprod Health, 6*, 18.

Betran, A. P., Merialdi, M., Lauer, J. A., Bing-Shun, W., Thomas, J., Van Look, P., & Wagner, M. (2007). Rates of caesarean section: analysis of global, regional and national estimates. *Paediatric and Perinatal Epidemiology, 21*(2), 98-113.

Beyerlein, A. a., Schiessl, B. a., Lack, N. a., & Von Kries, R. a. (2011). Associations of gestational weight loss with birth-related outcome: a retrospective cohort study. *BJOG: An International Journal of Obstetrics & Gynaecology, 118*(1), 55-61.

Bhopal, R., Rahemtulla, T., & Sheikh, A. (2005). Persistent high stroke mortality in Bangladeshi populations. *BMJ, 331*(7525), 1096-1097.

Bjorntorp, P. (1997). Obesity. *Lancet, 350*(9075), 423-426.

Blondel, B., Dutilh, P., Delour, M., & Uzan, S. (1993). Poor antenatal care and pregnancy outcome. *European Journal of Obstetrics & Gynecology and Reproductive Biology, 50*(3), 191-196.

Bodnar, L. M., Catov, J. M., Klebanoff, M. A., Ness, R. B., & Roberts, J. M. (2007). Prepregnancy body mass index and the occurrence of severe hypertensive disorders of pregnancy. *Epidemiology, 18*(2), 234-239.

Bodnar, L. M., Catov, J. M., & Roberts, J. M. (2007). Racial/ethnic differences in the monthly variation of preeclampsia incidence. *American Journal of Obstetrics & Gynecology, 196*(4), 324.e321-325.

Bodnar, L. M., Ness, R. B., Harger, G. F., & Roberts, J. M. (2005). Inflammation and triglycerides partially mediate the effect of prepregnancy body mass index on the risk of preeclampsia. *American Journal of Epidemiology, 162*(12), 1198-1206.

Bodnar, L. M., Ness, R. B., Markovic, N., & Roberts, J. M. (2005). The risk of preeclampsia rises with increasing prepregnancy body mass index. *Annals of Epidemiology, 15*(7), 475-482.

Bodnar, L. M., Siega-Riz, A. M., Simhan, H. N., Diesel, J. C., & Abrams, B. (2010). The Impact of Exposure Misclassification on Associations Between Prepregnancy BMI and Adverse Pregnancy Outcomes. *Obesity, 18*(11), 2184-2190.

Boers, K. E., Bijlenga, D., Mol, B. W., LeCessie, S., Birnie, E., van Pampus, M. G., . . . Scherjon, S. A. (2007). Disproportionate Intrauterine Growth Intervention Trial At Term: DIGITAT. *BMC Pregnancy Childbirth, 7*, 12.

Boers, K. E., Vijgen, S. M., Bijlenga, D., van der Post, J. A., Bekedam, D. J., Kwee, A., . . . on behalf of the DIGITAT study group. (2010). Induction versus expectant monitoring for intrauterine growth restriction at term: randomised equivalence trial (DIGITAT). *BMJ, 341*, c7087.

Bonari, L., Pinto, N., Ahn, E., Einarson, A., Steiner, M., & Koren, G. (2004). Perinatal risks of untreated depression during pregnancy. *Canadian Journal of Psychiatry, 49*(11), 726-735.

Boney, C. M., Verma, A., Tucker, R., & Vohr, B. R. (2005). Metabolic syndrome in childhood: association with birth weight, maternal obesity, and gestational diabetes mellitus. *Pediatrics, 115*(3), e290-296.

Boulet, S. L., Salihu, H. M., & Alexander, G. R. (2004). Mode of delivery and birth outcomes of macrosomic infants. *Journal of Obstetrics & Gynaecology, 24*(6), 622-629.

Boulvain, M., Senat, M.-V., Rozenberg, P., & Irion, O. (2012). Induction of labor or expectant management for large-for-dates fetuses: a randomized controlled trial. *American Journal of Obstetrics & Gynecology, 206*(1 Suppl), 2-2.

Bragg, F., Cromwell, D. A., Edozien, L. C., Gurol-Urganci, I., Mahmood, T. A., Templeton, A., & van der Meulen, J. H. (2010). Variation in rates of caesarean section among English NHS trusts after accounting for maternal and clinical risk: cross sectional study. *BMJ, 341*.

Brown, M. A., Lindheimer, M. D., de Swiet, M., Van Assche, A., & Moutquin, J. M. (2001). The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). *Hypertension in Pregnancy, 20*(1), IX-XIV.

Bruss, M. B., Morris, J. R., Dannison, L. L., Orbe, M. P., Quitugua, J. A., & Palacios, R. T. (2005). Food, culture, and family: exploring the coordinated management of meaning regarding childhood obesity. *Health Communication, 18*(2), 155-175.

Bryant, A. S., Washington, S., Kuppermann, M., Cheng, Y. W., & Caughey, A. B. (2009). Quality and equality in obstetric care: racial and ethnic differences in caesarean section delivery rates. *Paediatric and Perinatal Epidemiology, 23*(5), 454-462.

Buchwald, H., Avidor, Y., Braunwald, E., Jensen, M. D., Pories, W., Fahrbach, K., & Schoelles, K. (2004). Bariatric surgery: a systematic review and meta-analysis. *JAMA, 292*(14), 1724-1737.

Buhimschi, C., Buhimschi, I. A., Malinow, A. M., & Weiner, C. P. (2004). Intrauterine pressure during the second stage of labor in obese women. *Obstetrics & Gynecology, 103*, 225-230.

Bujold, E., Roberge, S., Lacasse, Y., Bureau, M., Audibert, F., Marcoux, S., . . . Giguere, Y. (2010). Prevention of preeclampsia and intrauterine growth restriction with aspirin started in early pregnancy: a meta-analysis. *Obstetrics & Gynecology, 116*(2 Pt 1), 402-414.

Bukowski, R., Uchida, T., Smith, G. C., Malone, F. D., Ball, R. H., Nyberg, D. A., . . . for the First and Second Trimester Evaluation of Risk (FASTER) Research Consortium. (2008). Individualized Norms of Optimal Fetal Growth: Fetal Growth Potential. *Obstetrics & Gynecology, 111*(5), 1065-1076.

Bullen, C., Tipene-Leach, D., Vander Hoorn, S., Jackson, R., Norton, R., & MacMahon, S. (1996). Ethnic differences in blood pressure: findings from the Fletcher Challenge-Auckland University Heart and Health Study. *New Zealand Medical Journal, 109*(1032), 395-397.

Callaway, L. K., O'Callaghan, M., & McIntyre, H. D. (2009). Obesity and the hypertensive disorders of pregnancy. *Hypertension in Pregnancy, 28*(4), 473-493.

Callister, P., Didham, R., & Kivi, A. (2009). *Who are we? The conceptualisation and expression of ethnicity. Official Statistics Research Series, 4.* Wellington, New Zealand: Statistics New Zealand. Retrieved from http://www.statisphere.govt.nz/official-statisticsresearch/series/default.htm

Camarano, L., Alkon, A., Nachtigall, R. D., Schembri, M., Weiss, S., & Croughan, M. S. (2012). Preterm delivery and low birth weight in singleton pregnancies conceived by women with and without a history of infertility. *Fertility & Sterility, 98*(3), 681-686 e681.

Carberry, A. E., Gordon, A., Bond, D. M., Hyett, J., Raynes-Greenow, C. H., & Jeffery, H. E. (2011). Customised versus population-based growth charts as a screening tool for detecting small for gestational age infants in low-risk pregnant women. *Cochrane Database of Systematic Reviews,* (12). doi:10.1002/14651858.CD008549.pub2 Retrieved from http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD008549/frame.html

Care Study Group. (2008). Maternal caffeine intake during pregnancy and risk of fetal growth restriction: a large prospective observational study. *BMJ, 337*, a2332.

Carmichael, S., Abrams, B., & Selvin, S. (1997). The pattern of maternal weight gain in women with good pregnancy outcomes. *American Journal of Public Health, 87*(12), 1984-1988.

Carreno, C. A., Clifton, R. G., Hauth, J. C., Myatt, L., Roberts, J. M., Spong, C. Y., . . . Sorokin, Y. (2012). Excessive Early Gestational Weight Gain and Risk of Gestational Diabetes Mellitus in Nulliparous Women. *Obstetrics & Gynecology, 119*(6), 1227-1233.

Carroli, G., Merialdi, M., Wojdyla, D., Abalos, E., Campodonico, L., Yao, S. E., . . . Van Look, P. (2010). Effects of calcium supplementation on uteroplacental and fetoplacental blood flow in low-calcium-intake mothers: a randomized controlled trial. *American Journal of Obstetrics & Gynecology, 202*(1), 45 e41-49.

Catalano, P. M. (2007). Management of obesity in pregnancy. *Obstetrics & Gynecology, 109*(2 Pt 1), 419-433.

Catalano, P. M., & Ehrenberg, H. M. (2006). The short- and long-term implications of maternal obesity on the mother and her offspring. *BJOG, 113*(10), 1126-1133.

Catalano, P. M., & Hauguel-De Mouzon, S. (2011). Is it time to revisit the Pedersen hypothesis in the face of the obesity epidemic? *American Journal of Obstetrics & Gynecology, 204*(6), 479-487.

Catalano, P. M., Thomas, A., Huston-Presley, L., & Amini, S. B. (2003). Increased fetal adiposity: a very sensitive marker of abnormal in utero development. *American Journal of Obstetrics & Gynecology, 189*(6), 1698-1704.

Catalano, P. M., Thomas, A. J., Huston, L. P., & Fung, C. M. (1998). Effect of maternal metabolism on fetal growth and body composition. *Diabetes Care, 21 Suppl 2*, B85-90.

Catov, J. M., Bodnar, L. M., Ness, R. B., Markovic, N., & Roberts, J. M. (2007). Association of periconceptional multivitamin use and risk of preterm or small-for-gestational-age births. *American Journal of Epidemiology, 166*(3), 296-303.

Caughey, A. B., Stotland, N. E., Washington, A. E., & Escobar, G. J. (2005). Maternal ethnicity, paternal ethnicity, and parental ethnic discordance: predictors of preeclampsia. *Obstetrics & Gynecology, 106*(1), 156-161.

Caughey, A. B., Stotland, N. E., Washington, A. E., & Escobar, G. J. (2009). Who is at risk for prolonged and postterm pregnancy? *American Journal of Obstetrics & Gynecology, 200*(6), 683.e681-685.

Cedergren, M. I. (2004). Maternal morbid obesity and the risk of adverse pregnancy outcome. *Obstetrics & Gynecology, 103*(2), 219-224.

Cedergren, M. I. (2006). Effects of gestational weight gain and body mass index on obstetric outcome in Sweden. *International Journal of Gynaecology & Obstetrics, 93*(3), 269-274.

Cedergren, M. I. (2007). Optimal gestational weight gain for body mass index categories. *Obstetrics & Gynecology, 110*(4), 759-764.

Cedergren, M. I. (2009). Non-elective caesarean delivery due to ineffective uterine contractility or due to obstructed labour in relation to maternal body mass index. *European Journal of Obstetrics, Gynecology, & Reproductive Biology, 145*(2), 163-166.

Centre for Maternal and Child Enquiries (CMACE). (2010). Maternal obesity in the UK: Findings from a national project. London: CMACE.

Ceriello, A., & Motz, E. (2004). Is oxidative stress the pathogenic mechanism underlying insulin resistance, diabetes, and cardiovascular disease? The common soil hypothesis revisited. *Arteriosclerosis, Thrombosis, and Vascular Biology, 24*(5), 816-823.

Challis, J. R., Lockwood, C. J., Myatt, L., Norman, J. E., Strauss, J. F., 3rd, & Petraglia, F. (2009). Inflammation and pregnancy. *Reproductive Sciences (Thousand Oaks, Calif), 16*(2), 206-215.

Chan, C. C., & To, W. W. (1999). Antepartum hemorrhage of unknown origin--what is its clinical significance? *Acta Obstetricia et Gynecologica Scandinavica, 78*(3), 186-190.

Chernausek, S. D. (2012). Update: consequences of abnormal fetal growth. *Journal of Clinical Endocrinology & Metabolism, 97*(3), 689-695.

Chien, P. F., Arnott, N., Gordon, A., Owen, P., & Khan, K. S. (2000). How useful is uterine artery Doppler flow velocimetry in the prediction of pre-eclampsia, intrauterine growth retardation and perinatal death? An overview. *BJOG, 107*(2), 196-208.

Chin, J. R., Henry, E., Holmgren, C. M., Varner, M. W., & Branch, D. W. (2012). Maternal obesity and contraction strength in the first stage of labor. *American Journal of Obstetrics & Gynecology, 207*(2), 129 e121-126.

Chiu, M., Austin, P. C., Manuel, D. G., Shah, B. R., & Tu, J. V. (2011). Deriving Ethnic-Specific BMI Cutoff Points for Assessing Diabetes Risk. *Diabetes Care, 34*(8), 1741-1748.

Chu, S. Y., Bachman, D. J., Callaghan, W. M., Whitlock, E. P., Dietz, P. M., Berg, C. J., . . . Hornbrook, M. C. (2008). Association between obesity during pregnancy and increased use of health care. *New England Journal of Medicine, 358*(14), 1444-1453.

Chu, S. Y., Kim, S. Y., Lau, J., Schmid, C. H., Dietz, P. M., Callaghan, W. M., & Curtis, K. M. (2007). Maternal obesity and risk of stillbirth: a metaanalysis. *American Journal of Obstetrics & Gynecology, 197*(3), 223-228.

Chung, J. H., Boscardin, W. J., Garite, T. J., Lagrew, D. C., & Porto, M. (2003). Ethnic differences in birth weight by gestational age: at least a partial explanation for the Hispanic epidemiologic paradox? *American Journal of Obstetrics & Gynecology, 189*(4), 1058-1062.

Chung, J. H., Garite, T. J., Kirk, A. M., Hollard, A. L., Wing, D. A., & Lagrew, D. C. (2006). Intrinsic racial differences in the risk of cesarean delivery are not explained by differences in caregivers or hospital site of delivery. *American Journal of Obstetrics & Gynecology, 194*(5), 1323-1328.

Church, T. S., Thomas, D. M., Tudor-Locke, C., Katzmarzyk, P. T., Earnest, C. P., Rodarte, R. Q., . . . Bouchard, C. (2011). Trends over 5 decades in U.S. occupation-related physical activity and their associations with obesity. *PLoS ONE, 6*(5), e19657.

Clausen, T., Burski, T. K., Oyen, N., Godang, K., Bollerslev, J., & Henriksen, T. (2005). Maternal anthropometric and metabolic factors in the first half of pregnancy and risk of neonatal macrosomia in term pregnancies. A prospective study. *European Journal of Endocrinology, 153*(6), 887-894.

Clausson, B., Cnattingius, S., & Axelsson, O. (1998). Preterm and term births of small for gestational age infants: a population-based study of risk factors among nulliparous women. *British Journal of Obstetrics & Gynaecology, 105*(9), 1011-1017.

Clausson, B., Gardosi, J., Francis, A., & Cnattingius, S. (2001). Perinatal outcome in SGA births defined by customised versus population-based birthweight standards. *BJOG: An International Journal of Obstetrics & Gynaecology, 108*(8), 830-834.

Cnattingius, S. (2004). The epidemiology of smoking during pregnancy: smoking prevalence, maternal characteristics, and pregnancy outcomes. *Nicotine & Tobacco Research, 6 Suppl 2*, S125-140.

Cnattingius, S., Bergstrom, R., Lipworth, L., & Kramer, M. S. (1998). Prepregnancy weight and the risk of adverse pregnancy outcomes. *New England Journal of Medicine, 338*(3), 147-152.

Cnattingius, S., Villamor, E., Lagerros, Y. T., Wikstrom, A. K., & Granath, F. (2012). High birth weight and obesity-a vicious circle across generations. *International Journal of Obesity, 36*(10), 1320-1324.

Cockram, C. S., Woo, J., Lau, E., Chan, J. C., Chan, A. Y., Lau, J., . . . Donnan, S. P. (1993). The prevalence of diabetes mellitus and impaired glucose tolerance among Hong Kong Chinese adults of working age. *Diabetes Research & Clinical Practice, 21*(1), 67-73.

Colin Bell, A., Adair, L. S., & Popkin, B. M. (2002). Ethnic differences in the association between body mass index and hypertension. *American Journal of Epidemiology, 155*(4), 346-353.

Coll, A. P., Yeo, G. S., Farooqi, I. S., & O'Rahilly, S. (2008). SnapShot: the hormonal control of food intake. *Cell, 135*(3), 572 e571-572.

Committee on Nutritional Status During Pregnancy and Lactation, & Institute of Medicine. (1990). *Nutrition During Pregnancy:Part I: Weight Gain, Part II: Nutrient Supplements*: The National Academies Press.

Conde-Agudelo, A., Rosas-Bermudez, A., & Kafury-Goeta, A. C. (2006). Birth spacing and risk of adverse perinatal outcomes: a meta-analysis. *JAMA, 295*(15), 1809-1823.

Considine, R. V., Sinha, M. K., Heiman, M. L., Kriauciunas, A., Stephens, T. W., Nyce, M. R., . . . Bauer, T. L. (1996). Serum immunoreactive-leptin concentrations in normal-weight and obese humans. *New England Journal of Medicine, 334*(5), 292-295.

Craig, B. M., & Adams, A. K. (2009). Accuracy of body mass index categories based on self-reported height and weight among women in the United States. *Maternal & Child Health Journal, 13*(4), 489-496.

Craig, E. D., Mantell, C. D., Ekeroma, A. J., Stewart, A. W., & Mitchell, E. A. (2004). Ethnicity and birth outcome: New Zealand trends 1980-2001. Part 1. Introduction, methods, results and overview. *Australian & New Zealand Journal of Obstetrics & Gynaecology, 44*(6), 530-536.

Crowther, C. A., Hiller, J. E., Moss, J. R., McPhee, A. J., Jeffries, W. S., Robinson, J. S., & Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) Trial Group. (2005). Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. *New England Journal of Medicine, 352*(24), 2477-2486.

Curhan, G. C., Chertow, G. M., Willett, W. C., Spiegelman, D., Colditz, G. A., Manson, J. E., . . . Stampfer, M. J. (1996). Birth weight and adult hypertension and obesity in women. *Circulation, 94*(6), 1310-1315.

D'Anna, R., Baviera, G., Corrado, F., Giordano, D., De Vivo, A., Nicocia, G., & Di Benedetto, A. (2006). Adiponectin and insulin resistance in early- and late-onset pre-eclampsia. *BJOG: An International Journal of Obstetrics & Gynaecology, 113*(11), 1264-1269.

Davis, T. M. (2008). Ethnic diversity in type 2 diabetes. *Diabetic Medicine, 25 Suppl 2*, 52-56.

Dekker, G. A. (1999). Risk factors for preeclampsia. *Clinical Obstetrics & Gynecology, 42*(3), 422-435.

Denison, F. C., Price, J., Graham, C., Wild, S., & Liston, W. A. (2008). Maternal obesity, length of gestation, risk of postdates pregnancy and spontaneous onset of labour at term. *BJOG: An International Journal of Obstetrics and Gynaecology, 115*(6), 720-725.

Despres, J. P. (1994). Dyslipidaemia and obesity. *Bailliere's Clinical Endocrinology and Metabolism, 8*(3), 629-660.

Despres, J. P., & Lemieux, I. (2006). Abdominal obesity and metabolic syndrome. *Nature, 444*(7121), 881-887.

Deurenberg-Yap, M., & Deurenberg, P. (2003). Is a re-evaluation of WHO body mass index cut-off values needed? The case of Asians in Singapore. *Nutrition Reviews, 61*(5 Pt 2), S80-87.

Deurenberg, P., Deurenberg-Yap, M., & Guricci, S. (2002). Asians are different from Caucasians and from each other in their body mass index/body fat per cent relationship. *Obesity Reviews, 3*(3), 141-146.

Deurenberg, P., Yap, M., & van Staveren, W. A. (1998). Body mass index and percent body fat: a meta analysis among different ethnic groups. *International Journal of Obesity & Related Metabolic Disorders: Journal of the International Association for the Study of Obesity, 22*(12), 1164-1171.

Di Cianni, G., Miccoli, R., Volpe, L., Lencioni, C., Ghio, A., Giovannitti, M. G., . . . Del Prato, S. (2005). Maternal triglyceride levels and newborn weight in pregnant women with normal glucose tolerance. *Diabetic Medicine, 22*(1), 21-25.

Dietz, P. M., Callaghan, W. M., Smith, R., & Sharma, A. J. (2009). Low pregnancy weight gain and small for gestational age: a comparison of the association using 3 different measures of small for gestational age. *American Journal of Obstetrics & Gynecology, 201*(1), 53 e51-57.

Dixit, A., & Girling, J. C. (2008). Obesity and pregnancy. *Journal of Obstetrics & Gynaecology, 28*(1), 14-23.

Dixon, J. B., Dixon, M. E., & O'Brien, P. E. (2005). Birth outcomes in obese women after laparoscopic adjustable gastric banding. *Obstetrics & Gynecology, 106*(5 Pt 1), 965-972.

Dixon, L., Aimer, P., Guilliland, K., Hendry, C., & Fletcher, L. (2009). Smoke Free Outcomes with Midwife Lead Maternity Carers: An analysis of smoking during pregnancy from the New Zealand College of Midwives Midwifery database 2004 - 2007. *New Zealand College of Midwives Journal*(40), 13-19.

Dodds, L., Fell, D. B., Joseph, K. S., Allen, V. M., & Butler, B. (2006). Outcomes of pregnancies complicated by hyperemesis gravidarum. *Obstetrics & Gynecology, 107*(2 Pt 1), 285-292.

Dorresteijn, J. A. N., Visseren, F. L. J., & Spiering, W. (2012). Mechanisms linking obesity to hypertension. *Obesity Reviews, 13*(1), 17-26.

Drewnowski, A. (1998). Energy density, palatability, and satiety: implications for weight control. *Nutrition Reviews, 56*(12), 347-353.

Drooger, J. C., Troe, J. W., Borsboom, G. J., Hofman, A., Mackenbach, J. P., Moll, H. A., . . . Joung, I. M. (2005). Ethnic differences in prenatal growth and the association with maternal and fetal characteristics. *Ultrasound in Obstetrics & Gynecology, 26*(2), 115-122.

Duckitt, K., & Harrington, D. (2005). Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. *BMJ, 330*(7491), 565.

Duley, L., Henderson-Smart, D. J., & Meher, S. (2006). Drugs for treatment of very high blood pressure during pregnancy. *Cochrane Database of Systematic Reviews*(3), CD001449.

Duley, L., Henderson-Smart, D. J., Meher, S., & King, J. F. (2007). Antiplatelet agents for preventing pre-eclampsia and its complications. *Cochrane Database of Systematic Reviews*(2), CD004659.

Eckel, R. H., Alberti, K. G., Grundy, S. M., & Zimmet, P. Z. (2010). The metabolic syndrome. *Lancet, 375*(9710), 181-183.

Eckel, R. H., Grundy, S. M., & Zimmet, P. Z. (2005). The metabolic syndrome. *Lancet, 365*(9468), 1415-1428.

Ecker, J. L., & Frigoletto, F. D., Jr. (2007). Cesarean delivery and the risk-benefit calculus. *New England Journal of Medicine, 356*(9), 885-888.

Egger, G., & Swinburn, B. A. (1997). An "ecological" approach to the obesity pandemic. *BMJ, 315*(7106), 477-480.

Ego, A., Subtil, D., Grange, G., Thiebaugeorges, O., Senat, M. V., Vayssiere, C., & Zeitlin, J. (2008). Should parity be included in customised fetal weight standards for identifying small-for-gestational-age babies? Results from a French multicentre study. *BJOG, 115*(10), 1256-1264.

Ehrenberg, H. M., Dierker, L., Milluzzi, C., & Mercer, B. M. (2002). Prevalence of maternal obesity in an urban center. *American Journal of Obstetrics & Gynecology, 187*(5), 1189-1193.

Ehrenberg, H. M., Durnwald, C. P., Catalano, P., & Mercer, B. M. (2004). The influence of obesity and diabetes on the risk of cesarean delivery. *American Journal of Obstetrics & Gynecology, 191*(3), 969-974.

Ehrenberg, H. M., Mercer, B. M., & Catalano, P. M. (2004). The influence of obesity and diabetes on the prevalence of macrosomia. *American Journal of Obstetrics & Gynecology, 191*(3), 964-968.

Ehrenthal, D. B., Jiang, X., & Strobino, D. M. (2010). Labor induction and the risk of a cesarean delivery among nulliparous women at term. *Obstetrics & Gynecology, 116*(1), 35-42.

Elder, K. A., & Wolfe, B. M. (2007). Bariatric surgery: a review of procedures and outcomes. *Gastroenterology, 132*(6), 2253-2271.

Empson, M., Lassere, M., Craig, J., & Scott, J. (2005). Prevention of recurrent miscarriage for women with antiphospholipid antibody or lupus anticoagulant. *Cochrane Database of Systematic Reviews*(2), CD002859.

Engeland, A., Bjorge, T., Selmer, R. M., & Tverdal, A. (2003). Height and body mass index in relation to total mortality. *Epidemiology, 14*(3), 293-299.

Feldt-Rasmussen, U., & Mathiesen, E. R. (2011). Endocrine disorders in pregnancy: physiological and hormonal aspects of pregnancy. *Best Practice & Research Clinical Endocrinology & Metabolism, 25*(6), 875-884.

Fergusson, D. M., Horwood, L. J., Northstone, K., & ALSPAC Study Team. (2002). Maternal use of cannabis and pregnancy outcome. *BJOG, 109*(1), 21-27.

Figueras, F., Figueras, J., Meler, E., Eixarch, E., Coll, O., Gratacos, E., . . . Carbonell, X. (2007). Customised birthweight standards accurately predict perinatal morbidity. *Archives of Disease in Childhood Fetal & Neonatal Edition, 92*(4), F277-280.

Figueras, F., & Gardosi, J. (2011). Intrauterine growth restriction: new concepts in antenatal surveillance, diagnosis, and management. *American Journal of Obstetrics & Gynecology*.

Finucane, M. M., Stevens, G. A., Cowan, M. J., Danaei, G., Lin, J. K., Paciorek, C. J., . . . on behalf of the Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group (Body Mass Index). (2011). National, regional, and global trends in body-mass index since

1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. *Lancet, 377*(9765), 557-567.

Flynn, J. (2012). The changing face of pediatric hypertension in the era of the childhood obesity epidemic. *Pediatr Nephrol*.

Freitas, P. F., Drachler Mde, L., Leite, J. C., & Marshall, T. (2009). Inequalities in cesarean delivery rates by ethnicity and hospital accessibility in Brazil. *International Journal of Gynaecology & Obstetrics, 107*(3), 198-201.

Fuglenes, D., Aas, E., Botten, G., Øian, P., & Kristiansen, I. S. (2012). Maternal Preference for Cesarean Delivery. *Obstetrics & Gynecology, 120*(2, Part 1), 252-260.

Fyfe, E. M., Anderson, N. H., North, R. A., Chan, E. H. Y., Taylor, R. S., Dekker, G. A., & McCowan, L. M. E. (2011). Risk of First-Stage and Second-Stage Cesarean Delivery by Maternal Body Mass Index Among Nulliparous Women in Labor at Term. *Obstetrics & Gynecology, 117*(6), 1315-1322.

Fyfe, E. M., Thompson, J. M., Anderson, N. H., Groom, K. M., & McCowan, L. M. (2012). Maternal obesity and postpartum haemorrhage after vaginal and caesarean delivery among nulliparous women at term: a retrospective cohort study. *BMC Pregnancy Childbirth, 12*(1), 112.

Galtier-Dereure, F., Boegner, C., & Bringer, J. (2000). Obesity and pregnancy: complications and cost. *American Journal of Clinical Nutrition, 71*(5 Suppl), 1242S-1248S.

Gardosi, J. (1994). Prediction of birthweight and fetal weight gain. In G. Chamberlain & J. Drife (Eds.), *Contemporary Reviews in Obstetrics & Gynaecology* (pp. 122-126): Parthenon.

Gardosi, J. (2004). Customized fetal growth standards: rationale and clinical application. *Seminars in Perinatology, 28*(1), 33-40.

Gardosi, J. (2005). Prematurity and fetal growth restriction. *Early Human Development, 81*(1), 43-49.

Gardosi, J. (2011). Clinical strategies for improving the detection of fetal growth restriction. *Clinics in Perinatology, 38*(1), 21-31, v.

Gardosi, J., Chang, A., Kalyan, B., Sahota, D., & Symonds, E. M. (1992). Customised antenatal growth charts. *Lancet, 339*(8788), 283-287.

Gardosi, J., Clausson, B., & Francis, A. (2007). The use of customised versus population-based birthweight standards in predicting perinatal mortality. *BJOG., 114*(10), 1301-1302; author reply 1303.

Gardosi, J., Clausson, B., & Francis, A. (2009). The value of customised centiles in assessing perinatal mortality risk associated with parity and maternal size. *BJOG: An International Journal of Obstetrics & Gynaecology, 116*(10), 1356-1363.

Gardosi, J., & Francis, A. (1999). Controlled trial of fundal height measurement plotted on customised antenatal growth charts. *British Journal of Obstetrics & Gynaecology, 106*(4), 309-317.

Gardosi, J., & Francis, A. (2009a). Adverse pregnancy outcome and association with small for gestational age birthweight by customized and population-based percentiles. *American Journal of Obstetrics & Gynecology, 201*(1), 28e21-28e28.

Gardosi, J., & Francis, A. (2009b). A customized standard to assess fetal growth in a US population. *American Journal of Obstetrics & Gynecology, 201*(1), 25.e21-27.

Gardosi, J., & Francis, A. (2009c). Parity and smallness for gestational age. *BJOG, 116*(8), 1135-1136; author reply 1136-1137.

Gardosi, J., & Francis, A. (2012a). Customised Antenatal Growth Chart. GROW version 8.7.41.0: Gestation Network,. Retrieved from www.gestation.net

Gardosi, J., & Francis, A. (2012b). Customised Weight Centile Calculator. GROW version 1.0: Gestation Network. Retrieved from www.gestation.net

Gardosi, J., & Francis, A. (2012c). *GROW documentation*. Birmingham: Perinatal Institute. Retrieved from https://www.gestation.net/literature.htm

Gardosi, J., Kady, S. M., McGeown, P., Francis, A., & Tonks, A. (2005). Classification of stillbirth by relevant condition at death (ReCoDe): population based cohort study. *BMJ, 331*(7525), 1113-1117.

Gardosi, J., Mongelli, M., & Mul, T. (1995). Intrauterine growth retardation. In E. A. P. Steegers, T. K. A. B. Eskes & E. M. Symonds (Eds.), *Bailliere's Clinical Obstetrics & Gynaecology: 'Preventive care in Obstetrics'* (pp. 445-463). London: Balliere Tindall.

Gardosi, J., Mongelli, M., Wilcox, M., & Chang, A. (1994). Screening and assessment of fetal growth. In H. P. van Geijn & F. Copray (Eds.), *A critical appraisal of fetal surveillance* (pp. 437-448). Amsterdam Elsevier.

Gardosi, J., Mongelli, M., Wilcox, M., & Chang, A. (1995). An adjustable fetal weight standard. *Ultrasound in Obstetrics & Gynecology, 6*(3), 168-174.

Gatrad, A. R., Ray, M., & Sheikh, A. (2004). Hindu birth customs. *Archives of Disease in Childhood, 89*(12), 1094-1097.

Gaudet, L. M., Gruslin, A., & Magee, L. A. (2011). Weight in pregnancy and its implications: what women report. *Journal of Obstetrics & Gynaecology Canada: JOGC, 33*(3), 227-234.

Getahun, D., Ananth, C. V., Oyelese, Y., Chavez, M. R., Kirby, R. S., & Smulian, J. C. (2007). Primary preeclampsia in the second pregnancy: effects of changes in prepregnancy body mass index between pregnancies. *Obstetrics & Gynecology, 110*(6), 1319-1325.

Getahun, D., Kaminsky, L. M., Elsasser, D. A., Kirby, R. S., Ananth, C. V., & Vintzileos, A. M. (2007). Changes in prepregnancy body mass index between pregnancies and risk of primary cesarean delivery. *American Journal of Obstetrics & Gynecology, 197*(4), 376.e371-377.

Getahun, D., Strickland, D., Lawrence, J. M., Fassett, M. J., Koebnick, C., & Jacobsen, S. J. (2009). Racial and ethnic disparities in the trends in primary cesarean delivery based on indications. *American Journal of Obstetrics & Gynecology, 201*(4), 422.e421-427.

Gilliam, M. (2006). Cesarean delivery on request: reproductive consequences. *Seminars in Perinatology, 30*(5), 257-260.

Gillman, M. W. (2005). Developmental origins of health and disease. *New England Journal of Medicine, 353*(17), 1848-1850.

Gluckman, P. D., & Hanson, M. A. (2004). Maternal constraint of fetal growth and its consequences. *Seminars in Fetal and Neonatal Medicine, 9*(5), 419-425.

Gluckman, P. D., & Hanson, M. A. (2008). Developmental and epigenetic pathways to obesity: an evolutionary-developmental perspective. *International Journal of Obesity, 32 Suppl 7*, S62-71.

Gonzalez-Bulnes, A., & Ovilo, C. (2012). Genetic basis, nutritional challenges and adaptive responses in the prenatal origin of obesity and type-2 diabetes. *Current Diabetes Reviews, 8*(2), 144-154.

Grassi, A. E., & Giuliano, M. A. (2000). The neonate with macrosomia. *Clinical Obstetrics & Gynecology, 43*(2), 340-348.

Gray, D. S., & Fujioka, K. (1991). Use of relative weight and Body Mass Index for the determination of adiposity. *Journal of Clinical Epidemiology, 44*(6), 545-550.

Gregory, K. D., & Korst, L. M. (2003). Age and racial/ethnic differences in maternal, fetal, and placental conditions in laboring patients. *American Journal of Obstetrics & Gynecology, 188*(6), 1602-1606; discussion 1606-1608.

Grey, C., Wells, S., Riddell, T., Kerr, A., Gentles, D., Pylypchuk, R., . . . Jackson, R. J. (2010). A comparative analysis of the cardiovascular disease risk factor profiles of Pacific peoples and Europeans living in New Zealand assessed in routine primary care: PREDICT CVD-11. *New Zealand Medical Journal, 123*(1309), 62-75.

Grindheim, G., Estensen, M.-E., Langesaeter, E., Rosseland, L. A., & Toska, K. (2012). Changes in blood pressure during healthy pregnancy: a longitudinal cohort study. *Journal of Hypertension, 30*(2), 342-350.

Grit Study Group. (2003). A randomised trial of timed delivery for the compromised preterm fetus: short term outcomes and Bayesian interpretation. *BJOG, 110*(1), 27-32.

Groom, K. M., North, R. A., Poppe, K. K., Sadler, L., & McCowan, L. M. E. (2007). The association between customised small for gestational age infants and pre-eclampsia or gestational hypertension varies with gestation at delivery. *BJOG: An International Journal of Obstetrics & Gynaecology, 114*(4), 478-484.

Groom, K. M., Poppe, K. K., North, R., & al., e. (2007). Small-for-gestational-age infants classified by customized or population birthweight centiles: impact of gestational age at delivery. *American Journal of Obstetrics & Gynecology, 197*, 239e231-239e235.

Gulmezoglu, A. M., Crowther, C. A., & Middleton, P. (2006). Induction of labour for improving birth outcomes for women at or beyond term. *Cochrane Database Syst Rev.*(4), CD004945.

Gunatilake, R. P., & Perlow, J. H. (2011). Obesity and pregnancy: clinical management of the obese gravida. *American Journal of Obstetrics & Gynecology, 204*(2), 106-119.

Guo, S. S., Zeller, C., Chumlea, W. C., & Siervogel, R. M. (1999). Aging, body composition, and lifestyle: the Fels Longitudinal Study. *American Journal of Clinical Nutrition, 70*(3), 405-411.

Habli, M., Levine, R. J., Qian, C., & Sibai, B. (2007). Neonatal outcomes in pregnancies with preeclampsia or gestational hypertension and in normotensive pregnancies that delivered at 35, 36, or 37 weeks of gestation. *American Journal of Obstetrics & Gynecology, 197*(4), 406 e401-407.

Hadlock, F. P., Harrist, R. B., & Martinez-Poyer, J. (1991). In utero analysis of fetal growth: a sonographic weight standard. *Radiology, 181*(1), 129-133.

Haeri, S., Khoury, J., Kovilam, O., & Miodovnik, M. (2008). The association of intrauterine growth abnormalities in women with type 1 diabetes mellitus complicated by vasculopathy. *American Journal of Obstetrics & Gynecology, 199*(3), 278 e271-275.

Haider, B. A., & Bhutta, Z. A. (2006). Multiple-micronutrient supplementation for women during pregnancy. *Cochrane Database of Systematic Reviews,* (4). doi:10.1002/14651858.CD004905.pub2 Retrieved from http://onlinelibrary.wiley.com/store/10.1002/14651858.CD004905.pub2/asset/CD004905.pdf?v=1&t=h9erpk9c&s=553784e55a424905ace09b1661a187c86dc674c9

Hainer, V., Toplak, H., & Stich, V. (2009). Fat or fit: what is more important? *Diabetes Care, 32 Suppl 2*, S392-397.

Halldorsson, T. I., Meltzer, H. M., Thorsdottir, I., Knudsen, V., & Olsen, S. F. (2007). Is high consumption of fatty fish during pregnancy a risk factor for fetal growth retardation? A study of 44,824 Danish pregnant women. *American Journal of Epidemiology, 166*(6), 687-696.

Halliday, H. L. (2009). Neonatal management and long-term sequelae. *Best Practice & Research in Clinical Obstetrics & Gynaecology, 23*(6), 871-880.

Han, T. S., Lean, M. E., & Seidell, J. C. (1996). Waist circumference remains useful predictor of coronary heart disease. *BMJ, 312*(7040), 1227-1228.

Hannah, M. E., Hannah, W. J., Hewson, S. A., Hodnett, E. D., Saigal, S., & Willan, A. R. (2000). Planned caesarean section versus planned vaginal birth for breech presentation at term: a randomised multicentre trial. Term Breech Trial Collaborative Group. *Lancet, 356*(9239), 1375-1383.

Hansen, A. K., Wisborg, K., Uldbjerg, N., & Henriksen, T. B. (2008). Risk of respiratory morbidity in term infants delivered by elective caesarean section: cohort study. *BMJ, 336*(7635), 85-87.

HAPO Study Cooperative Research Group. (2010). Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) Study: associations with maternal body mass index. *BJOG: An International Journal of Obstetrics & Gynaecology, 117*(5), 575-584.

HAPO Study Cooperative Research Group, Metzger, B. E., Lowe, L. P., Dyer, A. R., Trimble, E. R., Chaovarindr, U., . . . Sacks, D. A. (2008). Hyperglycemia and adverse pregnancy outcomes. *New England Journal of Medicine, 358*(19), 1991-2002.

Harmon, K. A., Gerard, L., Jensen, D. R., Kealey, E. H., Hernandez, T. L., Reece, M. S., . . . Bessesen, D. H. (2011). Continuous glucose profiles in obese and normal-weight pregnant women on a controlled diet: metabolic determinants of fetal growth. *Diabetes Care, 34*(10), 2198-2204.

Harris, R., Robson, B., Curtis, E., Purdie, G., Cormack, D., & Reid, P. (2007). Maori and non-Maori differences in caesarean section rates: a national review. *New Zealand Medical Journal, 120*(1250), U2444.

Haslam, D. W., & James, W. P. T. (2005). Obesity. *Lancet, 366*(9492), 1197-1209.

Hastings, G., Stead, M., McDermott, L., Forsyth, A., MacKintosh, A. M., Rayner, M., . . . Angus, K. (2003). *Review of research on the effects of food promotion to children. Final Report. Preparted for the Food Standards Agency*. Glasgow: The University of Strathclyde. Retrieved from http://food.gov.uk/multimedia/pdfs/foodpromotiontochildren1.pdf

Hedderson, M., Ehrlich, S., Sridhar, S., Darbinian, J., Moore, S., & Ferrara, A. (2012). Racial/Ethnic Disparities in the Prevalence of Gestational Diabetes Mellitus by BMI. *Diabetes Care, 35*(7), 1492-1498.

Heerwagen, M. J., Miller, M. R., Barbour, L. A., & Friedman, J. E. (2010). Maternal obesity and fetal metabolic programming: a fertile epigenetic soil. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology, 299*(3), R711-722.

Heffner, L. J., Elkin, E., & Fretts, R. C. (2003). Impact of labor induction, gestational age, and maternal age on cesarean delivery rates. *Obstetrics & Gynecology, 102*(2), 287-293.

Heinonen, S., & Kirkinen, P. (2000). Pregnancy outcome after previous stillbirth resulting from causes other than maternal conditions and fetal abnormalities. *Birth, 27*(1), 33-37.

Helmerhorst, F. M., Perquin, D. A. M., Donker, D., & Keirse, M. J. N. C. (2004). Perinatal outcome of singletons and twins after assisted conception: a systematic review of controlled studies. *BMJ, 328*(7434), 261.

Henderson, J., Gray, R., & Brocklehurst, P. (2007). Systematic review of effects of low-moderate prenatal alcohol exposure on pregnancy outcome. *BJOG, 114*(3), 243-252.

Henriksen, T. (2008). The macrosomic fetus: a challenge in current obstetrics. *Acta Obstetricia et Gynecologica Scandinavica, 87*(2), 134-145.

Henson, M. C., & Castracane, V. D. (2000). Leptin in pregnancy. *Biology of Reproduction, 63*(5), 1219-1228.

Henson, M. C., & Castracane, V. D. (2006). Leptin in pregnancy: an update. *Biology of Reproduction, 74*(2), 218-229.

Hepburn, M., & Rosenberg, K. (1986). An audit of the detection and management of small-for-gestational age babies. *British Journal of Obstetrics & Gynaecology, 93*(3), 212-216.

Herman, C. P., & Polivy, J. (2008). External cues in the control of food intake in humans: the sensory-normative distinction. *Physiology and Behavior, 94*(5), 722-728.

Hermann, G. M., Dallas, L. M., Haskell, S. E., & Roghair, R. D. (2010). Neonatal macrosomia is an independent risk factor for adult metabolic syndrome. *Neonatology, 98*(3), 238-244.

Herrera, B. M., & Lindgren, C. M. (2010). The genetics of obesity. *Current Diabetes Reports, 10*(6), 498-505.

Herrera, E., & Ortega-Senovilla, H. (2010). Disturbances in lipid metabolism in diabetic pregnancy - Are these the cause of the problem? *Best Practice & Research Clinical Endocrinology & Metabolism, 24*(4), 515-525.

Heslehurst, N., Ells, L. J., Simpson, H., Batterham, A., Wilkinson, J., & Summerbell, C. D. (2007). Trends in maternal obesity incidence rates, demographic predictors, and health inequalities in 36,821 women over a 15-year period. *BJOG: An International Journal of Obstetrics & Gynaecology, 114*(2), 187-194.

Heslehurst, N., Lang, R., Rankin, J., Wilkinson, J. R., & Summerbell, C. D. (2007). Obesity in pregnancy: a study of the impact of maternal obesity on NHS maternity services. *BJOG: An International Journal of Obstetrics & Gynaecology, 114*(3), 334-342.

Heslehurst, N., Simpson, H., Ells, L. J., Rankin, J., Wilkinson, J., Lang, R., . . . Summerbell, C. D. (2008). The impact of maternal BMI status on pregnancy outcomes with immediate short-term obstetric resource implications: a meta-analysis. *Obesity Reviews, 9*(6), 635-683.

Hessol, N. A., & Fuentes-Afflick, E. (2005). Ethnic differences in neonatal and postneonatal mortality. *Pediatrics, 115*(1), e44-51.

Hills, F. A., English, J., & Chard, T. (1996). Circulating levels of IGF-I and IGF-binding protein-1 throughout pregnancy: relation to birthweight and maternal weight. *Journal of Endocrinology, 148*(2), 303-309.

Hodge, A. M., Maple-Brown, L., Cunningham, J., Boyle, J., Dunbar, T., Weeramanthri, T., . . . O'Dea, K. (2010). Abdominal obesity and other risk factors largely explain the high CRP in indigenous Australians relative to the general population, but not gender differences: a cross-sectional study. *BMC Public Health, 10*, 700.

Hofmeyr, G. J., Lawrie, T. A., Atallah, A. N., & Duley, L. (2010). Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. *Cochrane Database of Systematic Reviews*(8), CD001059.

Hollis-Moffatt, J. E., Xu, X., Dalbeth, N., Merriman, M. E., Topless, R., Waddell, C., . . . Merriman, T. R. (2009). Role of the urate transporter SLC2A9 gene in susceptibility to gout in New Zealand Māori, Pacific Island, and Caucasian case–control sample sets. *Arthritis and Rheumatism, 60*(11), 3485-3492.

Hotamisligil, G. S. (2006). Inflammation and metabolic disorders. *Nature, 444*(7121), 860-867.

Howarth, C., Gazis, A., & James, D. (2007). Associations of Type 1 diabetes mellitus, maternal vascular disease and complications of pregnancy. *Diabetic Medicine, 24*(11), 1229-1234.

Human Rights Commission. (2012). *A fair go for all? Rite tahi tātou katoa? Addressing Structural Discrimination in Public Services*. New Zealand: Human Rights Commission.

Huppertz, B. (2008). Placental origins of preeclampsia: challenging the current hypothesis. *Hypertension, 51*(4), 970-975.

Hutcheon, J. A., Walker, M., & Platt, R. W. (2010). Assessing the Value of Customized Birth Weight Percentiles. *American Journal of Epidemiology, 173*(4), 459-467.

Hutcheon, J. A., Zhang, X., Cnattingius, S., Kramer, M. S., & Platt, R. W. (2008). Customised birthweight percentiles: does adjusting for maternal characteristics matter? *BJOG: An International Journal of Obstetrics & Gynaecology, 115*(11), 1397-1404.

Hutcheon, J. A., Zhang, X., & Platt, R. W. (2009). The benefits of customizing for maternal factors or the benefits of using an intrauterine standard at preterm ages? *American Journal of Obstetrics & Gynecology, 199*, e18-e19.

Hutcheon, J. A., Zhang, X., Platt, R. W., Cnattingius, S., & Kramer, M. S. (2011). The case against customised birthweight standards. *Paediatric and Perinatal Epidemiology, 25*(1), 11-16.

Ibison, J. M. (2005). Ethnicity and mode of delivery in 'low-risk' first-time mothers, East London, 1988-1997. *European Journal of Obstetrics, Gynecology, & Reproductive Biology, 118*(2), 199-205.

Irion, O., & Boulvain, M. (1998). Induction of labour for suspected fetal macrosomia. *Cochrane Database of Systematic Reviews*(2), CD000938.

Irwin, D. E., Savitz, D. A., Hertz-Picciotto, I., & St Andre, K. A. (1994). The risk of pregnancy-induced hypertension: black and white differences in a military population. *American Journal of Public Health, 84*(9), 1508-1510.

Jaddoe, V. W., Bakker, R., Hofman, A., Mackenbach, J. P., Moll, H. A., Steegers, E. A., & Witteman, J. C. (2007). Moderate alcohol consumption during pregnancy and the risk of low birth weight and preterm birth. The generation R study. *Annals of Epidemiology, 17*(10), 834-840.

James, W. P. T. (2008). The epidemiology of obesity: the size of the problem. *Journal of Internal Medicine, 263*(4), 336-352.

James, W. P. T., Jackson-Leach, R., Ni Mhurchu, C., Kalamara, E., Shayeghi, M., Rigby, N. J., . . . Rodgers, A. (2004). Overweight and obesity (high body mass index). In L. A. Ezzati M, Rodgers A, Murray CJL, (Ed.), *Comparative Quantification of Health Risks: Global and Regional Burden of Disease Attributable to Selected Major Risk Factors* (Vol. 1). Geneva: World Health Organization.

Jaquet, D., Swaminathan, S., Alexander, G. R., Czernichow, P., Collin, D., Salihu, H. M., . . . Levy-Marchal, C. (2005). Significant paternal contribution to the risk of small for gestational age. *BJOG, 112*(2), 153-159.

Jensen, H., Agger, A. O., & Rasmussen, K. L. (2000). Interventions during labor in relation to height in obese women. *Zentralblatt fur Gynakologie, 122*(7), 395-396.

Johnson, E. B., Reed, S. D., Hitti, J., & Batra, M. (2005). Increased risk of adverse pregnancy outcome among Somali immigrants in Washington state. *American Journal of Obstetrics & Gynecology, 193*(2), 475-482.

Johnson, N. P., Lewis, J., & Ansell, D. A. (1995). Does ethnicity influence obstetric intervention? *New Zealand Medical Journal, 108*(1013), 511-512.

Kabir, A. A., Pridjian, G., Steinmann, W. C., Herrera, E. A., & Khan, M. M. (2005). Racial differences in cesareans: an analysis of U.S. 2001 National Inpatient Sample Data. *Obstetrics & Gynecology, 105*(4), 710-718.

Kanagalingam, M. G., Forouhi, N. G., Greer, I. A., & Sattar, N. (2005). Changes in booking body mass index over a decade: retrospective analysis from a Glasgow Maternity Hospital. *BJOG: An International Journal of Obstetrics & Gynaecology, 112*(10), 1431-1433.

Kandraju, H., Agrawal, S., Geetha, K., Sujatha, L., Subramanian, S., & Murki, S. (2012). Gestational age-specific centile charts for anthropometry at birth for South Indian infants. *Indian Pediatr, 49*(3), 199-202.

Kaufmann, P., Black, S., & Huppertz, B. (2003). Endovascular trophoblast invasion: implications for the pathogenesis of intrauterine growth retardation and preeclampsia. *Biology of Reproduction, 69*(1), 1-7.

Kelly, Y., Panico, L., Bartley, M., Marmot, M., Nazroo, J., & Sacker, A. (2009). Why does birthweight vary among ethnic groups in the UK? Findings from the Millennium Cohort Study. *Journal of Public Health, 31*(1), 131-137.

Kenealy, T., Elley, C. R., Robinson, E., Bramley, D., Drury, P. L., Kerse, N. M., . . . Arroll, B. (2008). An association between ethnicity and cardiovascular outcomes for people with Type 2 diabetes in New Zealand. *Diabetic Medicine, 25*(11), 1302-1308.

Khan, K. S., Wojdyla, D., Say, L., Gülmezoglu, A. M., & Van Look, P. F. A. (2006). WHO analysis of causes of maternal death: a systematic review. *The Lancet, 367*(9516), 1066-1074.

Kharb, S., & Singh, G. P. (2001). Hyperuricemia, oxidative stress in preeclampsia. *Clinica Chimica Acta, 305*(1-2), 201-203.

Kho, E. M., McCowan, L. M. E., North, R. A., Roberts, C. T., Chan, E., Black, M. A., . . . on behalf of the SCOPE Consortium. (2009). Duration of sexual relationship and its effect on preeclampsia and small for gestational age perinatal outcome. *Journal of Reproductive Immunology, 82*(1), 66-73.

Kierans, W. J., Joseph, K. S., Luo, Z.-C., Platt, R., Wilkins, R., & Kramer, M. S. (2008). Does one size fit all? The case for ethnic-specific standards of fetal growth. *BMC Pregnancy & Childbirth, 8*, 1.

Kita, T., Kume, N., Minami, M., Hayashida, K., Murayama, T., Sano, H., . . . Yokode, M. (2001). Role of oxidized LDL in atherosclerosis. *Ann N Y Acad Sci, 947*, 199-205; discussion 205-196.

Klebanoff, M. A., Levine, R. J., Clemens, J. D., & Wilkins, D. G. (2002). Maternal serum caffeine metabolites and small-for-gestational age birth. *American Journal of Epidemiology, 155*(1), 32-37.

Kleijer, M. E., Dekker, G. A., & Heard, A. R. (2005). Risk factors for intrauterine growth restriction in a socio-economically disadvantaged region. *Journal of Maternal-Fetal & Neonatal Medicine, 18*(1), 23-30.

Klonoff-Cohen, H. S., Cross, J. L., & Pieper, C. F. (1996). Job stress and preeclampsia. *Epidemiology, 7*(3), 245-249.

Knight, M., Kurinczuk, J. J., Spark, P., Brocklehurst, P., & Ukoss. (2009). Inequalities in maternal health: national cohort study of ethnic variation in severe maternal morbidities. *BMJ, 338*, b542.

Ko, G. T., Chan, J. C., Cockram, C. S., & Woo, J. (1999). Prediction of hypertension, diabetes, dyslipidaemia or albuminuria using simple anthropometric indexes in Hong Kong Chinese. *International Journal of Obesity & Related Metabolic Disorders: Journal of the International Association for the Study of Obesity, 23*(11), 1136-1142.

Koifman, A., Levy, A., Zaulan, Y., Harlev, A., Mazor, M., Wiznitzer, A., & Sheiner, E. (2008). The clinical significance of bleeding during the second trimester of pregnancy. *Archives of Gynecology & Obstetrics, 278*(1), 47-51.

Koopmans, C. M., Bijlenga, D., Groen, H., Vijgen, S. M., Aarnoudse, J. G., Bekedam, D. J., . . . for the Hypitat study group. (2009). Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation (HYPITAT): a multicentre, open-label randomised controlled trial. *Lancet, 374*(9694), 979-988.

Kral, J. G., Biron, S., Simard, S., Hould, F. S., Lebel, S., Marceau, S., & Marceau, P. (2006). Large maternal weight loss from obesity surgery prevents transmission of obesity to children who were followed for 2 to 18 years. *Pediatrics, 118*(6), e1644-1649.

Kramer, M. S. (1987). Determinants of low birth weight: methodological assessment and meta-analysis. *Bulletin of the World Health Organization, 65*(5), 663-737.

Kramer, M. S., Ananth, C. V., Platt, R. W., & Joseph, K. S. (2006). US Black vs White disparities in foetal growth: physiological or pathological? *International Journal of Epidemiology, 35*(5), 1187-1195.

Kramer, M. S., & Kakuma, R. (2003). Energy and protein intake in pregnancy. *Cochrane Database of Systematic Reviews*(4), CD000032.

Kramer, M. S., Platt, R., Yang, H., McNamara, H., & Usher, R. H. (1999). Are all growth-restricted newborns created equal(ly)? *Pediatrics, 103*(3), 599-602.

Kramer, M. S., Usher, R. H., Pollack, R., Boyd, M., & Usher, S. (1997). Etiologic determinants of abruptio placentae. *Obstetrics & Gynecology, 89*(2), 221-226.

Kuczmarski, R. J., & Flegal, K. M. (2000). Criteria for definition of overweight in transition: background and recommendations for the United States. *American Journal of Clinical Nutrition, 72*(5), 1074-1081.

Kupek, E., Petrou, S., Vause, S., & Maresh, M. (2002). Clinical, provider and sociodemographic predictors of late initiation of antenatal care in England and Wales. *BJOG: An International Journal of Obstetrics & Gynaecology, 109*(3), 265-273.

La Merrill, M., Stein, C. R., Landrigan, P., Engel, S. M., & Savitz, D. A. (2011). Prepregnancy body mass index, smoking during pregnancy, and infant birth weight. *Annals of Epidemiology, 21*(6), 413-420.

LaCoursiere, D. Y., Bloebaum, L., Duncan, J. D., & Varner, M. W. (2005). Population-based trends and correlates of maternal overweight and obesity, Utah 1991-2001. *American Journal of Obstetrics & Gynecology, 192*(3), 832-839.

Landau, R. L. (1983). The appetite of pregnant women. *JAMA, 250*(24), 3323.

Landsbergis, P. A., & Hatch, M. C. (1996). Psychosocial work stress and pregnancy-induced hypertension. *Epidemiology, 7*(4), 346-351.

Lang, J. M., Cohen, A., & Lieberman, E. (1992). Risk factors for small-for-gestational-age birth in a preterm population. *American Journal of Obstetrics & Gynecology, 166*(5), 1374-1378.

Lang, J. M., Lieberman, E., & Cohen, A. (1996). A comparison of risk factors for preterm labor and term small-for-gestational-age birth. *Epidemiology, 7*(4), 369-376.

Langer, O. (2000). Fetal macrosomia: etiologic factors. *Clinical Obstetrics & Gynecology, 43*(2), 283-297.

Larkin, J. C., Hill, L. M., Speer, P. D., & Simhan, H. N. (2012). Risk of Morbid Perinatal Outcomes in Small-for-Gestational-Age Pregnancies: Customized Compared With Conventional Standards of Fetal Growth. *Obstetrics & Gynecology, 119*(1), 21-27.

Lashen, H., Fear, K., & Sturdee, D. W. (2004). Obesity is associated with increased risk of first trimester and recurrent miscarriage: matched case-control study. *Human Reproduction, 19*(7), 1644-1646.

Lavebratt, C., Almgren, M., & Ekstrom, T. J. (2012). Epigenetic regulation in obesity. *International Journal of Obesity, 36*(6), 757-765.

Lean, M. E., Han, T. S., & Morrison, C. E. (1995). Waist circumference as a measure for indicating need for weight management. *BMJ, 311*(6998), 158-161.

Leddy, M. A., Power, M. L., & Schulkin, J. (2008). The impact of maternal obesity on maternal and fetal health. *Reviews in Obstetrics and Gynecology, 1*(4), 170-178.

Leung, T. Y., Leung, T. N., Sahota, D. S., Chan, O. K., Chan, L. W., Fung, T. Y., & Lau, T. K. (2008). Trends in maternal obesity and associated risks of adverse pregnancy outcomes in a population of Chinese women. *BJOG: An International Journal of Obstetrics & Gynaecology, 115*(12), 1529-1537.

Li, Z., Zhang, Y., Ying Ma, J., Kapoun, A. M., Shao, Q., Kerr, I., . . . Pollitt, N. S. (2007). Recombinant vascular endothelial growth factor 121 attenuates hypertension and improves kidney damage in a rat model of preeclampsia. *Hypertension, 50*(4), 686-692.

Liamputtong, P., Yimyam, S., Parisunyakul, S., Baosoung, C., & Sansiriphun, N. (2005). Traditional beliefs about pregnancy and child birth among women from Chiang Mai, Northern Thailand. *Midwifery, 21*(2), 139-153.

Lin, H. C., Sheen, T. C., Tang, C. H., & Kao, S. (2004). Association between maternal age and the likelihood of a cesarean section: a population-based multivariate logistic regression analysis. *Acta Obstetricia et Gynecologica Scandinavica, 83*(12), 1178-1183.

Lindqvist, P. G., & Molin, J. (2005). Does antenatal identification of small-for-gestational age fetuses significantly improve their outcome? *Ultrasound in Obstetrics & Gynecology, 25*(3), 258-264.

Liston, F., & Davies, G. A. (2011). Thromboembolism in the obese pregnant woman. *Semin Perinatol, 35*(6), 330-334.

Loetscher, K. C., Selvin, S., Zimmermann, R., & Abrams, B. (2007). Ethnic-cultural background, maternal body size and pregnancy outcomes in a diverse Swiss cohort. *Women & Health, 45*(2), 25-40.

Low, J. A., Handley-Derry, M. H., Burke, S. O., Peters, R. D., Pater, E. A., Killen, H. L., & Derrick, E. J. (1992). Association of intrauterine fetal growth retardation and learning deficits at age 9 to 11 years. *American Journal of Obstetrics & Gynecology, 167*(6), 1499-1505.

Low, P., Paterson, J., Wouldes, T., Carter, S., Williams, M., & Percival, T. (2005). Factors affecting antenatal care attendance by mothers of Pacific infants living in New Zealand. *New Zealand Medical Journal, 118*(1216), U1489.

Lowe, S. A., Brown, M. A., Dekker, G. A., Gatt, S., McLintock, C., McMahon, L., . . . Walters, B. (2008). Guidelines for the management of hypertensive disorders of pregnancy 2008.

Lowe, S. A., Brown, M. A., Dekker, G. A., Gatt, S., McLintock, C. K., McMahon, L. P., . . . Walters, B. (2009). Guidelines for the management of hypertensive disorders of pregnancy 2008. *Australian & New Zealand Journal of Obstetrics & Gynaecology, 49*(3), 242-246.

Lumbiganon, P., Laopaiboon, M., Gulmezoglu, A. M., Souza, J. P., Taneepanichskul, S., Ruyan, P., . . . for the World Health Organization Global Survey on Maternal and Perinatal Health Research Group. (2010). Method of delivery and pregnancy outcomes in Asia: the WHO global survey on maternal and perinatal health 2007-08. *Lancet, 375*(9713), 490-499.

MacDorman, M. F., Menacker, F., & Declercq, E. (2008). Cesarean birth in the United States: epidemiology, trends, and outcomes. *Clinics in Perinatology, 35*(2), 293-307.

Magnus, P., Bakketeig, L. S., & Skjaerven, R. (1993). Correlations of birth weight and gestational age across generations. *Annals of Human Biology, 20*(3), 231-238.

Maimbolwa, M. C., Yamba, B., Diwan, V., & Ransjo-Arvidson, A.-B. (2003). Cultural childbirth practices and beliefs in Zambia. *Journal of Advanced Nursing, 43*(3), 263-274.

Makgoba, M., Savvidou, M. D., & Steer, P. J. (2012). The effect of maternal characteristics and gestational diabetes on birthweight. *BJOG: An International Journal of Obstetrics & Gynaecology, 119*(9), 1091-1097.

Makrides, M., & Crowther, C. A. (2001). Magnesium supplementation in pregnancy. *Cochrane Database of Systematic Reviews*(4), CD000937.

Makrides, M., Duley, L., & Olsen, S. F. (2006). Marine oil, and other prostaglandin precursor, supplementation for pregnancy uncomplicated by pre-eclampsia or intrauterine growth restriction. *Cochrane Database of Systematic Reviews*(3), CD003402.

Mantell, C. D., Craig, E. D., Stewart, A. W., Ekeroma, A. J., & Mitchell, E. A. (2004). Ethnicity and birth outcome: New Zealand trends 1980-2001: Part 2. Pregnancy outcomes for Maori women. *Australian & New Zealand Journal of Obstetrics & Gynaecology, 44*(6), 537-540.

Marcoux, S., Berube, S., Brisson, C., & Mondor, M. (1999). Job strain and pregnancy-induced hypertension. *Epidemiology, 10*(4), 376-382.

Mbah, A. K., Kornosky, J. L., Kristensen, S., August, E. M., Alio, A. P., Marty, P. J., . . . Salihu, H. M. (2010). Super-obesity and risk for early and late pre-eclampsia. *BJOG: An International Journal of Obstetrics & Gynaecology, 117*(8), 997-1004.

McCormack, R. A., Doherty, D. A., Magann, E. F., Hutchinson, M., & Newnham, J. P. (2008). Antepartum bleeding of unknown origin in the second half of pregnancy and pregnancy outcomes. *BJOG: An International Journal of Obstetrics & Gynaecology, 115*(11), 1451-1457.

McCowan, L. M. E., Buist, R. G., North, R. A., & Gamble, G. (1996). Perinatal morbidity in chronic hypertension. *British Journal of Obstetrics & Gynaecology, 103*(2), 123-129.

McCowan, L. M. E., Dekker, G. A., Chan, E., Stewart, A. W., Chappell, L. C., Hunter, M., . . . on behalf of the SCOPE consortium. (2009). Spontaneous preterm birth and small for gestational age infants in women who stop smoking early in pregnancy: prospective cohort study. *BMJ, 338*, b1081.

McCowan, L. M. E., Harding, J. E., & Stewart, A. W. (2005). Customised birthweight centiles predict SGA pregnancies with perinatal morbidity. *BJOG: An International Journal of Obstetrics & Gynaecology, 112*(8), 1026-1033.

McCowan, L. M. E., & Horgan, R. P. (2009). Risk factors for small for gestational age infants. *Best Practice & Research in Clinical Obstetrics & Gynaecology, 23*(6), 779-793.

McCowan, L. M. E., North, R. A., Kho, E. M., Black, M. A., Chan, E. H. Y., Dekker, G. A., . . . Roberts, C. T. (2011). Paternal contribution to small for gestational age babies: a multicenter prospective study. *Obesity, 19*(5), 1035-1039.

McCowan, L. M. E., Roberts, C. T., Dekker, G. A., Taylor, R. S., Chan, E. H., Kenny, L. C., . . . on behalf of the SCOPE consortium. (2010). Risk factors for small-for-gestational-age infants by customised birthweight centiles: data from an international prospective cohort study. *BJOG, 117*(13), 1599-1607.

McCowan, L. M. E., & Stewart, A. W. (2004). Term birthweight centiles for babies from New Zealand's main ethnic groups. *Australian & New Zealand Journal of Obstetrics & Gynaecology, 44*(5), 432-435.

McCowan, L. M. E., Stewart, A. W., Francis, A., & Gardosi, J. (2004). A customised birthweight centile calculator developed for a New Zealand population. *Australian & New Zealand Journal of Obstetrics & Gynaecology, 44*(5), 428-431.

McDonald, S. D., Han, Z., Mulla, S., & Beyene, J. (2010). Overweight and obesity in mothers and risk of preterm birth and low birth weight infants: systematic review and meta-analyses. *BMJ, 341*, c3428.

McGuinness, B. J., & Trivedi, A. N. (1999). Maternal height as a risk factor for Caesarean section due to failure to progress in labour. *Australian & New Zealand Journal of Obstetrics & Gynaecology, 39*(2), 152-154.

McIntyre, H. D., Gibbons, K. S., Flenady, V. J., & Callaway, L. K. (2012). Overweight and obesity in Australian mothers: epidemic or endemic? *Medical Journal of Australia, 196*(3), 184-188.

McKeigue, P. M., Miller, G. J., & Marmot, M. G. (1989). Coronary heart disease in south Asians overseas: a review. *Journal of Clinical Epidemiology, 42*(7), 597-609.

McKeigue, P. M., Shah, B., & Marmot, M. G. (1991). Relation of central obesity and insulin resistance with high diabetes prevalence and cardiovascular risk in South Asians. *Lancet, 337*(8738), 382-386.

McMillen, I. C., Adams, M. B., Ross, J. T., Coulter, C. L., Simonetta, G., Owens, J. A., . . . Edwards, L. J. (2001). Fetal growth restriction: adaptations and consequences. *Reproduction, 122*(2), 195-204.

Meis, P. J., Michielutte, R., Peters, T. J., Wells, H. B., Sands, R. E., Coles, E. C., & Johns, K. A. (1995). Factors associated with preterm birth in Cardiff, Wales. I. Univariable and multivariable analysis. *American Journal of Obstetrics & Gynecology, 173*(2), 590-596.

Meltzer, H. M., Brantsaeter, A. L., Nilsen, R. M., Magnus, P., Alexander, J., & Haugen, M. (2011). Effect of dietary factors in pregnancy on risk of pregnancy complications: results from

the Norwegian Mother and Child Cohort Study. *American Journal of Clinical Nutrition, 94*(6 Suppl), 1970S-1974S.

Mikkelsen, T. B., Osler, M., Orozova-Bekkevold, I., Knudsen, V. K., & Olsen, S. F. (2006). Association between fruit and vegetable consumption and birth weight: a prospective study among 43,585 Danish women. *Scandinavian Journal of Public Health, 34*(6), 616-622.

Mikolajczyk, R. T., Zhang, J., Betran, A. P., Souza, J. P., Mori, R., Gulmezoglu, A. M., & Merialdi, M. (2011). A global reference for fetal-weight and birthweight percentiles. *Lancet, 377*(9780), 1855-1861.

Milagro, F. I., Mansego, M. L., De Miguel, C., & Martinez, J. A. (2012). Dietary factors, epigenetic modifications and obesity outcomes: Progresses and perspectives. *Molecular Aspects of Medicine*.

Ministry of Health. (2004a). *Ethnicity Data Protocols for the Health and Disability Sector*. Wellington: Ministry of Health. Retrieved from http://www.nzhis.govt.nz/documentation/ethnicity/index.html

Ministry of Health. (2004b). Tracking the Obesity Epidemic: New Zealand 1977-2003. Wellington: Ministry of Health.

Ministry of Health. (2008). A Portrait of Health. Key Results of the 2006/07 New Zealand Health Survey. Wellington: Ministry of Health.

Ministry of Health. (2009a). *Clinical Guidelines for Weight Management in New Zealand Adults.* Wellington: Ministry of Health.

Ministry of Health. (2009b). *Tobacco Trends 2008: A brief update of tobacco use in New Zealand.* (HP number: 4798). Wellington: Ministry of Health,Retrieved from www.moh.govt.nz.

Ministry of Health. (2010). Living Standards and Health: New Zealand 2006/07. Wellington: Ministry of Health.

Ministry of Health. (2011). Maternity Snapshot 2010, Retrieved from http://www.health.govt.nz/publication/maternity-snapshot-2010-provisional-data.

Minkoff, H., & Chervenak, F. A. (2003). Elective primary cesarean delivery. *New England Journal of Medicine, 348*(10), 946-950.

Mistry, H. D., McCallum, L. A., Kurlak, L. O., Greenwood, I. A., Broughton Pipkin, F., & Tribe, R. M. (2011). Novel expression and regulation of voltage-dependent potassium channels in placentas from women with preeclampsia. *Hypertension, 58*(3), 497-504.

Mitchell, E. A., Robinson, E., Clark, P. M., Becroft, D. M., Glavish, N., Pattison, N. S., . . . Wild, C. J. (2004). Maternal nutritional risk factors for small for gestational age babies in a developed country: a case-control study. *Archives of Disease in Childhood Fetal & Neonatal Edition, 89*(5), F431-435.

Modder J, Fitzsimons KJ, & on behalf of the Centre for Maternal and Child Enquiries and the Royal College of Obstetricians and Gynaecologists. (2010). CMACE/RCOG Joint Guideline: Management of Women with Obesity in Pregnancy: Centre for Maternal and Child Enquiries and the Royal College of Obstetricians and Gynaecologists.

Mongelli, M., & Gardosi, J. (1996). Gestation-adjusted projection of estimated fetal weight. *Acta Obstetricia et Gynecologica Scandinavica, 75*(1), 28-31.

Mongelli, M., & Gardosi, J. (1999). Symphysis-fundus height and pregnancy characteristics in ultrasound-dated pregnancies. *Obstetrics & Gynecology, 94*(4), 591-594.

Mongraw-Chaffin, M. L., Cirillo, P. M., & Cohn, B. A. (2010). Preeclampsia and cardiovascular disease death: prospective evidence from the child health and development studies cohort. *Hypertension, 56*(1), 166-171.

Montan, S. (2007). Increased risk in the elderly parturient. *Current Opinion in Obstetrics & Gynecology, 19*(2), 110-112.

Moodley, J., & Daya, P. (1994). Eclampsia: a continuing problem in developing countries. *International Journal of Gynaecology & Obstetrics, 44*(1), 9-14.

Morken, N. H., Kallen, K., & Jacobsson, B. (2006). Fetal growth and onset of delivery: a nationwide population-based study of preterm infants. *American Journal of Obstetrics & Gynecology, 195*(1), 154-161.

Morning, A. (2008). Ethnic Classification in Global Perspective: A Cross-National Survey of the 2000 Census Round. *Population Research and Policy Review, 27*(2), 239-272.

Morrison, J., Williams, G. M., Najman, J. M., & Andersen, M. J. (1991). The influence of paternal height and weight on birth-weight. *Australian & New Zealand Journal of Obstetrics & Gynaecology, 31*(2), 114-116.

Morrison, J. J., Rennie, J. M., & Milton, P. J. (1995). Neonatal respiratory morbidity and mode of delivery at term: influence of timing of elective caesarean section. *British Journal of Obstetrics & Gynaecology, 102*(2), 101-106.

Moynihan, A. T., Hehir, M. P., Glavey, S. V., Smith, T. J., & Morrison, J. J. (2006). Inhibitory effect of leptin on human uterine contractility in vitro. *American Journal of Obstetrics & Gynecology, 195*(2), 504-509.

Müller, M. J., Lagerpusch, M., Enderle, J., Schautz, B., Heller, M., & Bosy-Westphal, A. (2012). Beyond the body mass index: tracking body composition in the pathogenesis of obesity and the metabolic syndrome. *Obesity Reviews, 13*, 6-13.

Myatt, L., Clifton, R. G., Roberts, J. M., Spong, C. Y., Hauth, J. C., Varner, M. W., . . . for the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units (MFMU) Network. (2012). First-trimester prediction of preeclampsia in nulliparous women at low risk. *Obstetrics & Gynecology, 119*(6), 1234-1242.

Myles, T. D., Gooch, J., & Santolaya, J. (2002). Obesity as an independent risk factor for infectious morbidity in patients who undergo cesarean delivery. *Obstetrics & Gynecology, 100*(5 Pt 1), 959-964.

Nagy, S., Bush, M., Stone, J., Lapinski, R. H., & Gardo, S. (2003). Clinical significance of subchorionic and retroplacental hematomas detected in the first trimester of pregnancy. *Obstetrics & Gynecology, 102*(1), 94-100.

Nanayakkara, K. K., Samarakoon, A. B., Perera, B. H., De Silva, A. W. S. S., & Nanayakkara, C. D. (2011). Size of Sri Lankan newborns at birth. *Journal of Obstetrics & Gynaecology, 31*(4), 311-314.

Nath, C. A., Ananth, C. V., DeMarco, C., Vintzileos, A. M., & for the New Jersey-Placental Abruption Study Investigators. (2008). Low birthweight in relation to placental abruption and maternal thrombophilia status. *American Journal of Obstetrics & Gynecology, 198*(3), 293 e291-295.

National Center for Health Statistics. (2011). *Health, United States, 2010: With Special Feature on Death and Dying*. Hyattsville, MD.

National Institute for Health and Clinical Excellence. (2010). *Weight management before, during and after pregnancy. PH27*. Retrieved from http://guidance.nice.org.uk/PH27

National Women's Health, A. D. H. B. (2008). *National Women's Annual Clinical Report 2007*. Auckland: National Women's Health, Auckland District Health Board. Retrieved from http://www.adhb.govt.nz/nwhealthinfo

National Women's Health, A. D. H. B. (2012). *National Women's Annual Clinical Report 2011*. Auckland, New Zealand: National Women's Health, Auckland District Health Board. Retrieved from http://www.adhb.govt.nz/nwhealthinfo

Neilson, J. P. (2003). Interventions for treating placental abruption. *Cochrane Database of Systematic Reviews*(1), CD003247.

Nelson, R. L., Furner, S. E., Westercamp, M., & Farquhar, C. (2010). Cesarean delivery for the prevention of anal incontinence. *Cochrane Database of Systematic Reviews,* (2). Retrieved from http://onlinelibrary.wiley.com/store/10.1002/14651858.CD006756.pub2/asset/CD006756.pdf?v=1&t=h8xk5mf1&s=f713e21c6e9adf6558e22ebf09664ea557d62a06

Ness, R. B., & Sibai, B. M. (2006). Shared and disparate components of the pathophysiologies of fetal growth restriction and preeclampsia. *American Journal of Obstetrics & Gynecology, 195*(1), 40-49.

Nohr, E. A., Vaeth, M., Baker, J. L., Sorensen, T., Olsen, J., & Rasmussen, K. M. (2008). Combined associations of prepregnancy body mass index and gestational weight gain with the outcome of pregnancy. *American Journal of Clinical Nutrition, 87*(6), 1750-1759.

Nohr, E. A., Vaeth, M., Baker, J. L., Sorensen, T. I., Olsen, J., & Rasmussen, K. M. (2009). Pregnancy outcomes related to gestational weight gain in women defined by their body mass index, parity, height, and smoking status. *American Journal of Clinical Nutrition, 90*(5), 1288-1294.

Nold, J. L., & Georgieff, M. K. (2004). Infants of diabetic mothers. *Pediatric Clinics of North America, 51*(3), 619-637, viii.

North, R. A., McCowan, L. M., Dekker, G. A., Poston, L., Chan, E. H., Stewart, A. W., . . . Kenny, L. C. (2011). Clinical risk prediction for pre-eclampsia in nulliparous women: development of model in international prospective cohort. *BMJ, 342*, d1875.

Nuthalapaty, F. S., Rouse, D. J., & Owen, J. (2004). The association of maternal weight with cesarean risk, labor duration, and cervical dilation rate during labor induction. *Obstetrics & Gynecology, 103*(3), 452-456.

O'Brien, T. E., Ray, J. G., & Chan, W. S. (2003). Maternal body mass index and the risk of preeclampsia: a systematic overview. *Epidemiology, 14*(3), 368-374.

Odegard, R. A., Vatten, L. J., Nilsen, S. T., Salvesen, K. A., & Austgulen, R. (2000). Risk factors and clinical manifestations of pre-eclampsia. *BJOG, 107*(11), 1410-1416.

Odibo, A. O., Francis, A., Cahill, A. G., Macones, G. A., Crane, J. P., & Gardosi, J. (2010). Association between pregnancy complications and small-for-gestational-age birth weight defined by customized fetal growth standard versus a population-based standard. *Journal of Maternal-Fetal & Neonatal Medicine*.

Odibo, A. O., Nelson, D., Stamilio, D. M., Sehdev, H. M., & Macones, G. A. (2006). Advanced maternal age is an independent risk factor for intrauterine growth restriction. *American Journal of Perinatology, 23*(5), 325-328.

Ogden, C. L., Carroll, M. D., Kit, B. K., & Flegal, K. M. (2012). Prevalence of obesity and trends in body mass index among US children and adolescents, 1999-2010. *JAMA, 307*(5), 483-490.

Oken, E., Kleinman, K. P., Olsen, S. F., Rich-Edwards, J. W., & Gillman, M. W. (2004). Associations of seafood and elongated n-3 fatty acid intake with fetal growth and length of gestation: results from a US pregnancy cohort. *American Journal of Epidemiology, 160*(8), 774-783.

Olsen, S. F., Halldorsson, T. I., Willett, W. C., Knudsen, V. K., Gillman, M. W., Mikkelsen, T. B., . . . and the Nutrix Consortium. (2007). Milk consumption during pregnancy is associated with increased infant size at birth: prospective cohort study. *American Journal of Clinical Nutrition, 86*(4), 1104-1110.

Olsen, S. F., Olsen, J., & Frische, G. (1990). Does fish consumption during pregnancy increase fetal growth? A study of the size of the newborn, placental weight and gestational age in relation to fish consumption during pregnancy. *Int J Epidemiol, 19*(4), 971-977.

Ong, K. (2006). Size at birth, postnatal growth and risk of obesity. *Hormone Research, 65 Suppl 3*, 65-69.

Ong, K., Kratzsch, J., Kiess, W., Costello, M., Scott, C., & Dunger, D. (2000). Size at birth and cord blood levels of insulin, insulin-like growth factor I (IGF-I), IGF-II, IGF-binding protein-1 (IGFBP-1), IGFBP-3, and the soluble IGF-II/mannose-6-phosphate receptor in term human infants. The ALSPAC Study Team. Avon Longitudinal Study of Pregnancy and Childhood. *Journal of Clinical Endocrinology & Metabolism, 85*(11), 4266-4269.

Orskou, J., Kesmodel, U., Henriksen, T. B., & Secher, N. J. (2001). An increasing proportion of infants weigh more than 4000 grams at birth. *Acta Obstetricia et Gynecologica Scandinavica, 80*(10), 931-936.

Owen, C. G., Martin, R. M., Whincup, P. H., Smith, G. D., & Cook, D. G. (2005). Effect of infant feeding on the risk of obesity across the life course: a quantitative review of published evidence. *Pediatrics, 115*(5), 1367-1377.

Owen, P., Ogah, J., Bachmann, L. M., & Khan, K. S. (2003). Prediction of intrauterine growth restriction with customised estimated fetal weight centiles. *BJOG, 110*(4), 411-415.

Owens, L. A., O'Sullivan, E. P., Kirwan, B., Avalos, G., Gaffney, G., Dunne, F., for the Atlantic Dip Collaborators. (2010). ATLANTIC DIP: the impact of obesity on pregnancy outcome in glucose-tolerant women. *Diabetes Care, 33*(3), 577-579.

Ozturk, E., Balat, O., Pehlivan, S., Ugur, M. G., & Sever, T. (2011). Genetic variation of myeloperoxidase gene contributes to preeclampsia: a preliminary association study in Turkish population. *Hypertension in Pregnancy, 30*(4), 377-383.

Paarlberg, K. M., Vingerhoets, A. J., Passchier, J., Dekker, G. A., Heinen, A. G., & van Geijn, H. P. (1999). Psychosocial predictors of low birthweight: a prospective study. *British Journal of Obstetrics & Gynaecology, 106*(8), 834-841.

Pain, S., Chang, A. M., Flenady, V., & Chan, F. Y. (2006). Customised birthweight: coefficients for an Australian population and validation of the model. *Australian & New Zealand Journal of Obstetrics & Gynaecology, 46*(5), 388-394.

Palaniappan, L. P., Wong, E. C., Shin, J. J., Fortmann, S. P., & Lauderdale, D. S. (2011). Asian Americans have greater prevalence of metabolic syndrome despite lower body mass index. *International Journal of Obesity, 35*(3), 393-400.

Pang, M. W., Leung, T. N., Sahota, D. S., Lau, T. K., & Chang, A. M. (2000). Development of a customised birthweight standard for ethnic Chinese subjects. *Australian & New Zealand Journal of Obstetrics & Gynaecology, 40*(2), 161-164.

Pantham, P., Askelund, K. J., & Chamley, L. W. (2011). Trophoblast deportation part II: a review of the maternal consequences of trophoblast deportation. *Placenta, 32*(10), 724-731.

Paranjothy, S., Frost, C., & Thomas, J. (2005). How much variation in CS rates can be explained by case mix differences? *BJOG: An International Journal of Obstetrics & Gynaecology, 112*(5), 658-666.

Park, A. J., & Bloom, S. R. (2005). Neuroendocrine control of food intake. *Current Opinion in Gastroenterology, 21*(2), 228-233.

Pasupathy, D., McCowan, L. M., Poston, L., Kenny, L. C., Dekker, G. A., North, R. A., for the SCOPE consortium. (2012). Perinatal Outcomes in Large Infants Using Customised Birthweight Centiles and Conventional Measures of High Birthweight. *Paediatric and Perinatal Epidemiology, 26*(6), 543-552.

Pearson, J. D. (2000). Normal endothelial cell function. *Lupus, 9*(3), 183-188.

Pietrobelli, A., Formica, C., Wang, Z., & Heymsfield, S. B. (1996). Dual-energy X-ray absorptiometry body composition model: review of physical concepts. *American Journal of Physiology, 271*(6 Pt 1), E941-951.

PMMRC. (2012). Sixth Annual Report of the Perinatal and Maternal Mortality Review Committee. Reporting Mortality 2010. Wellington: Health Quality and Safety Commission 2012.

Poehlman, E. T. (1992). Energy expenditure and requirements in aging humans. *Journal of Nutrition, 122*(11), 2057-2065.

Poobalan, A. S., Aucott, L. S., Gurung, T., Smith, W. C., & Bhattacharya, S. (2009). Obesity as an independent risk factor for elective and emergency caesarean delivery in nulliparous women--systematic review and meta-analysis of cohort studies. *Obesity Reviews, 10*(1), 28-35.

Poon, L. C., Syngelaki, A., Akolekar, R., Lai, J., & Nicolaides, K. H. (2012). Combined Screening for Preeclampsia and Small for Gestational Age at 11-13 Weeks. *Fetal Diagnosis and Therapy*.

Popkin, B. M., & Gordon-Larsen, P. (2004). The nutrition transition: worldwide obesity dynamics and their determinants. *International Journal of Obesity & Related Metabolic Disorders: Journal of the International Association for the Study of Obesity, 28 Suppl 3*, S2-9.

Poppitt, S. D., & Prentice, A. M. (1996). Energy density and its role in the control of food intake: evidence from metabolic and community studies. *Appetite, 26*(2), 153-174.

Poston, L., Briley, A. L., Seed, P. T., Kelly, F. J., Shennan, A. H., & Vitamins in Pre-eclampsia Trial, C. (2006). Vitamin C and vitamin E in pregnant women at risk for pre-eclampsia (VIP trial): randomised placebo-controlled trial. *Lancet, 367*(9517), 1145-1154.

Poston, L., & Chappell, L. C. (2012). How should women be advised on weight management in pregnancy? *BMJ, 344*, e2774.

Prentice, A. M., Goldberg, G. R., Jebb, S. A., Black, A. E., Murgatroyd, P. R., & Diaz, E. O. (1991). Physiological responses to slimming. *Proceedings of the Nutrition Society, 50*(2), 441-458.

Prentice, A. M., & Jebb, S. A. (1995). Obesity in Britain: gluttony or sloth? *BMJ, 311*(7002), 437-439.

Prins, J. B. (2002). Adipose tissue as an endocrine organ. *Best Practice & Research Clinical Endocrinology & Metabolism, 16*(4), 639-651.

Pryor, J. E., Thompson, J. M., Robinson, E., Clark, P. M., Becroft, D. M., Pattison, N. S., . . . Mitchell, E. A. (2003). Stress and lack of social support as risk factors for small-for-gestational-age birth. *Acta Paediatrica, 92*(1), 62-64.

Rajasingam, D., Seed, P. T., Briley, A. L., Shennan, A. H., & Poston, L. (2009). A prospective study of pregnancy outcome and biomarkers of oxidative stress in nulliparous obese women. *American Journal of Obstetrics & Gynecology, 200*(4), 395.e391-399.

Ramin, S. M., Vidaeff, A. C., Yeomans, E. R., & Gilstrap, L. C., 3rd. (2006). Chronic renal disease in pregnancy. *Obstetrics & Gynecology, 108*(6), 1531-1539.

Ramos, G. A., & Caughey, A. B. (2005). The interrelationship between ethnicity and obesity on obstetric outcomes. *American Journal of Obstetrics & Gynecology, 193*(3 Pt 2), 1089-1093.

Ramsay, J. E., Ferrell, W. R., Crawford, L., Wallace, A. M., Greer, I. A., & Sattar, N. (2002). Maternal obesity is associated with dysregulation of metabolic, vascular, and inflammatory pathways. *Journal of Clinical Endocrinology & Metabolism, 87*(9), 4231-4237.

Ramsay, J. E., Stewart, F., Greer, I. A., & Sattar, N. (2003). Microvascular dysfunction: a link between pre-eclampsia and maternal coronary heart disease. *BJOG, 110*(11), 1029-1031.

Rao, A. K., Cheng, Y. W., & Caughey, A. B. (2006). Perinatal complications among different Asian-American subgroups. *American Journal of Obstetrics & Gynecology, 194*(5), e39-41.

Rao, A. K., Daniels, K., El-Sayed, Y. Y., Moshesh, M. K., & Caughey, A. B. (2006). Perinatal outcomes among Asian American and Pacific Islander women. *American Journal of Obstetrics & Gynecology, 195*(3), 834-838.

Rasmussen, K. M., & Yaktine, A. L. (Eds.). (2009). *Weight Gain During Pregnancy: Reexamining the Guidelines*. Washington, D.C.: National Academies Press.

Raum, E., Arabin, B., Schlaud, M., Walter, U., & Schwartz, F. W. (2001). The impact of maternal education on intrauterine growth: a comparison of former West and East Germany. *Int J Epidemiol, 30*(1), 81-87.

Redman, C. W., & Sargent, I. L. (2003). Pre-eclampsia, the placenta and the maternal systemic inflammatory response--a review. *Placenta, 24 Suppl A*, S21-27.

Redman, C. W., & Sargent, I. L. (2010). Immunology of pre-eclampsia. *American Journal of Reproductive Immunology, 63*(6), 534-543.

Rissanen, A. M., Heliovaara, M., Knekt, P., Reunanen, A., & Aromaa, A. (1991). Determinants of weight gain and overweight in adult Finns. *European Journal of Clinical Nutrition, 45*(9), 419-430.

Robinson, C. J., Alanis, M. C., Wagner, C. L., Hollis, B. W., & Johnson, D. D. (2010). Plasma 25-hydroxyvitamin D levels in early-onset severe preeclampsia. *American Journal of Obstetrics & Gynecology, 203*(4), 366.e361-366.

Robinson, H. E., O'Connell, C. M., Joseph, K. S., & McLeod, N. L. (2005). Maternal outcomes in pregnancies complicated by obesity. *Obstetrics & Gynecology, 106*(6), 1357-1364.

Robson, S. J., Tan, W. S., Adeyemi, A., & Dear, K. B. G. (2009). Estimating the rate of cesarean section by maternal request: anonymous survey of obstetricians in Australia. *Birth, 36*(3), 208-212.

Roex, A., Nikpoor, P., van Eerd, E., Hodyl, N., & Dekker, G. (2012). Serial plotting on customised fundal height charts results in doubling of the antenatal detection of small for gestational age fetuses in nulliparous women. *Australian & New Zealand Journal of Obstetrics & Gynaecology, 52*(1), 78-82.

Rogers, I., Emmett, P., Ness, A., & Golding, J. (2004). Maternal fish intake in late pregnancy and the frequency of low birth weight and intrauterine growth retardation in a cohort of British infants. *Journal of Epidemiology & Community Health, 58*(6), 486-492.

Roman, H., Blondel, B., Breart, G., & Goffinet, F. (2008). Do risk factors for elective cesarean section differ from those of cesarean section during labor in low risk pregnancies? *Journal of Perinatal Medicine, 36*(4), 297-305.

Rosen, E. D., & Spiegelman, B. M. (2006). Adipocytes as regulators of energy balance and glucose homeostasis. *Nature, 444*(7121), 847-853.

Ross, R. (1999). Atherosclerosis: an inflammatory disease. *New England Journal of Medicine, 340*(2), 115-126.

Rouse, D. J., Owen, J., Goldenberg, R. L., & Cliver, S. P. (1996). The effectiveness and costs of elective cesarean delivery for fetal macrosomia diagnosed by ultrasound. *JAMA, 276*(18), 1480-1486.

Rowe, R. E., & Garcia, J. (2003). Social class, ethnicity and attendance for antenatal care in the United Kingdom: a systematic review. *Journal of Public Health Medicine, 25*(2), 113-119.

Rowlands, I., Graves, N., de Jersey, S., McIntyre, H. D., & Callaway, L. K. (2010). Obesity in pregnancy: outcomes and economics. *Seminars in Fetal and Neonatal Medicine, 15*(2), 94-99.

Royal College of Obstetricians and Gynaecologists. (2002). *The investigation and management of the small-for-gestational-age fetus. Green Top Guideline no. 31*. London: Royal College of Obstetricians and Gynaecologists. Retrieved from www.rcog.org.uk/files/rcogcorp/uploadedfiles/GT31SmallGestationalAgeFetus.pdf

Rumbold, A., Duley, L., Crowther, C. A., & Haslam, R. R. (2008). Antioxidants for preventing pre-eclampsia. *Cochrane Database of Systematic Reviews*(1), CD004227.

Rush, E. C., Plank, L. D., Chandu, V., Laulu, M., Simmons, D., Swinburn, B. A., & Yajnik, C. (2004). Body size, body composition, and fat distribution: a comparison of young New Zealand men of European, Pacific Island, and Asian Indian ethnicities. *New Zealand Medical Journal, 117*(1207), U1203.

Sadler, L. C., McCowan, L. M. E., & Stone, P. (2002). Associations between ethnicity and obstetric intervention in New Zealand. *New Zealand Medical Journal, 115*(1147), 36-39.

Sahota, D. S., Kagan, K. O., Lau, T. K., Leung, T. Y., & Nicolaides, K. H. (2008). Customized birth weight: coefficients and validation of models in a UK population. *Ultrasound in Obstetrics & Gynecology, 32*(7), 884-889.

Sanchez-Ramos, L., Bernstein, S., & Kaunitz, A. M. (2002). Expectant management versus labor induction for suspected fetal macrosomia: a systematic review. *Obstetrics & Gynecology, 100*(5 Pt 1), 997-1002.

Sanderson, D. A., Wilcox, M. A., & Johnson, I. R. (1994). The individualised birthweight ratio: a new method of identifying intrauterine growth retardation. *British Journal of Obstetrics & Gynaecology, 101*(4), 310-314.

Sassi, F. (2010). *Obesity and the economics of prevention: Fit not Fat*. France: OECD.

Scarborough, P., Burg, M. R., Foster, C., Swinburn, B. A., Sacks, G., Rayner, M., . . . Allender, S. (2011). Increased energy intake entirely accounts for increase in body weight in women but not in men in the UK between 1986 and 2000. *British Journal of Nutrition, 105*(9), 1399-1404.

Schempf, A. H., & Strobino, D. M. (2008). Illicit drug use and adverse birth outcomes: is it drugs or context? *Journal of Urban Health, 85*(6), 858-873.

Schwartz, M. W., Woods, S. C., Porte, D., Jr., Seeley, R. J., & Baskin, D. G. (2000). Central nervous system control of food intake. *Nature, 404*(6778), 661-671.

Schwartz, R. S. (2001). Racial profiling in medical research. *New England Journal of Medicine, 344*(18), 1392-1393.

Seed, P. T., Chappell, L. C., Black, M. A., Poppe, K. K., Hwang, Y.-C., Kasabov, N., . . . North, R. A. (2011). Prediction of Preeclampsia and Delivery of Small for Gestational Age Babies Based on a Combination of Clinical Risk Factors in High-Risk Women. *Hypertension in Pregnancy, 30*(1), 58-73.

Sewell, M. F., Huston-Presley, L., Super, D. M., & Catalano, P. (2006). Increased neonatal fat mass, not lean body mass, is associated with maternal obesity. *American Journal of Obstetrics & Gynecology, 195*(4), 1100-1103.

Shah, D., Tay, A., Desai, A., Parikh, M., Nauta, M., & Yoong, W. (2011). The obstetric performance of Chinese immigrants residing in the UK. *Journal of Obstetrics & Gynaecology, 31*(6), 480-482.

Shand, B., Elder, P., Scott, R., Poa, N., & Frampton, C. M. (2007). Comparison of plasma adiponectin levels in New Zealand Maori and Caucasian individuals. *New Zealand Medical Journal, 120*(1257), U2606.

Sheiner, E., Levy, A., Silverberg, D., Menes, T. S., Levy, I., Katz, M., & Mazor, M. (2004). Pregnancy after bariatric surgery is not associated with adverse perinatal outcome. *American Journal of Obstetrics & Gynecology, 190*(5), 1335-1340.

Shen, W., Punyanitya, M., Chen, J., Gallagher, D., Albu, J., Pi-Sunyer, X., . . . Heymsfield, S. B. (2006). Waist circumference correlates with metabolic syndrome indicators better than percentage fat. *Obesity, 14*(4), 727-736.

Sibai, B., Dekker, G., & Kupferminc, M. (2005). Pre-eclampsia. *Lancet, 365*(9461), 785-799.

Siega-Riz, A. M., Adair, L. S., & Hobel, C. J. (1994). Institute of Medicine maternal weight gain recommendations and pregnancy outcome in a predominantly Hispanic population. *Obstetrics & Gynecology, 84*(4), 565-573.

Simmons, G., Jackson, R., Swinburn, B., & Yee, R. L. (1996). The increasing prevalence of obesity in New Zealand: is it related to recent trends in smoking and physical activity? *New Zealand Medical Journal, 109*(1018), 90-92.

Simpson, S. A., Shaw, C., & McNamara, R. (2011). What is the most effective way to maintain weight loss in adults? *BMJ, 343*, d8042.

Singhal, A. (2006). Early nutrition and long-term cardiovascular health. *Nutrition Reviews, 64*(5 Pt 2), S44-49; discussion S72-91.

Smith, G. C. (2000). A population study of birthweight and the risk of caesarean section: Scotland 1980-1996. *BJOG: An International Journal of Obstetrics & Gynaecology, 107*(6), 740-744.

Smith, G. C., Cordeaux, Y., White, I. R., Pasupathy, D., Missfelder-Lobos, H., Pell, J. P., . . . Fleming, M. (2008). The effect of delaying childbirth on primary cesarean section rates. *PLoS Medicine / Public Library of Science, 5*(7), e144.

Smith, G. C., Pell, J. P., & Walsh, D. (2001). Pregnancy complications and maternal risk of ischaemic heart disease: a retrospective cohort study of 129,290 births. *Lancet, 357*(9273), 2002-2006.

Smith, G. C., Shah, I., White, I. R., Pell, J. P., & Dobbie, R. (2007). Previous preeclampsia, preterm delivery, and delivery of a small for gestational age infant and the risk of unexplained stillbirth in the second pregnancy: a retrospective cohort study, Scotland, 1992-2001. *American Journal of Epidemiology, 165*(2), 194-202.

Smith, G. D., Harding, S., & Rosato, M. (2000). Relation between infants' birth weight and mothers' mortality: prospective observational study. *BMJ, 320*(7238), 839-840.

Smith, J., Cianflone, K., Biron, S., Hould, F. S., Lebel, S., Marceau, S., . . . Marceau, P. (2009). Effects of maternal surgical weight loss in mothers on intergenerational transmission of obesity. *Journal of Clinical Endocrinology & Metabolism, 94*(11), 4275-4283.

Snijders, R. J., Sherrod, C., Gosden, C. M., & Nicolaides, K. H. (1993). Fetal growth retardation: associated malformations and chromosomal abnormalities. *American Journal of Obstetrics & Gynecology, 168*(2), 547-555.

Solomon, C. G., & Seely, E. W. (2006). Hypertension in pregnancy. *Endocrinology and Metabolism Clinics of North America, 35*(1), 157-171, vii.

Spinillo, A., Capuzzo, E., Piazzi, G., Nicola, S., Colonna, L., & Iasci, A. (1994). Maternal high-risk factors and severity of growth deficit in small for gestational age infants. *Early Human Development, 38*(1), 35-43.

Statistics New Zealand. (2004). *Report of the Review of the Measurement of Ethnicity*. Wellington, New Zealand: Statistics New Zealand.

Statistics New Zealand. (2005). *Statistical Standard for Ethnicity*. Wellington, New Zealand: Statistics New Zealand.

Stavrou, E. P., Ford, J. B., Shand, A. W., Morris, J. M., & Roberts, C. L. (2011). Epidemiology and trends for Caesarean section births in New South Wales, Australia: a population-based study. *BMC Pregnancy & Childbirth, 11*, 8.

Steinfeld, J. D., Valentine, S., Lerer, T., Ingardia, C. J., Wax, J. R., & Curry, S. L. (2000). Obesity-related complications of pregnancy vary by race. *Journal of Maternal-Fetal Medicine, 9*(4), 238-241.

Stephansson, O., Dickman, P. W., Johansson, A., & Cnattingius, S. (2001). Maternal weight, pregnancy weight gain, and the risk of antepartum stillbirth. *American Journal of Obstetrics & Gynecology, 184*(3), 463-469.

Stjernholm, Y. V., Petersson, K., & Eneroth, E. (2010). Changed indications for cesarean sections. *Acta Obstetricia et Gynecologica Scandinavica, 89*(1), 49-53.

Stone, P., Cook, D., Hutton, J., Purdie, G., Murray, H., & Harcourt, L. (1995). Measurements of blood pressure, oedema and proteinuria in a pregnant population of New Zealand. *Australian & New Zealand Journal of Obstetrics & Gynaecology, 35*(1), 32-37.

Stotland, N. E. (2008). Obesity and pregnancy. *BMJ, 337*, a2450.

Stratton, J. F., Scanaill, S. N., Stuart, B., & Turner, M. J. (1995). Are babies of normal birth weight who fail to reach their growth potential as diagnosed by ultrasound at increased risk? *Ultrasound in Obstetrics & Gynecology, 5*(2), 114-118.

Stronks, K., & Kunst, A. E. (2009). The complex interrelationship between ethnic and socio-economic inequalities in health. *J Public Health (Oxf), 31*(3), 324-325.

Surkan, P. J., Stephansson, O., Dickman, P. W., & Cnattingius, S. (2004). Previous preterm and small-for-gestational-age births and the subsequent risk of stillbirth. *New England Journal of Medicine, 350*(8), 777-785.

Swinburn, B. A., Ashton, T., Gillespie, J., Cox, B., Menon, A., Simmons, D., & Birkbeck, J. (1997). Health care costs of obesity in New Zealand. *International Journal of Obesity & Related Metabolic Disorders: Journal of the International Association for the Study of Obesity, 21*(10), 891-896.

Swinburn, B. A., Ley, S. J., Carmichael, H. E., & Plank, L. D. (1999). Body size and composition in Polynesians. *International Journal of Obesity & Related Metabolic Disorders: Journal of the International Association for the Study of Obesity, 23*(11), 1178-1183.

Swinburn, B. A., Sacks, G., Hall, K. D., McPherson, K., Finegood, D. T., Moodie, M. L., & Gortmaker, S. L. (2011). The global obesity pandemic: shaped by global drivers and local environments. *Lancet, 378*(9793), 804-814.

Swinburn, B. A., Sacks, G., & Ravussin, E. (2009). Increased food energy supply is more than sufficient to explain the US epidemic of obesity. *American Journal of Clinical Nutrition, 90*(6), 1453-1456.

Sze, E. H. M., Sherard, G. B., 3rd, & Dolezal, J. M. (2002). Pregnancy, labor, delivery, and pelvic organ prolapse. *Obstetrics & Gynecology, 100*(5 Pt 1), 981-986.

Tam, C. Y., Hislop, G., Hanley, A. J., Minkin, S., Boyd, N. F., & Martin, L. J. (2011). Food, beverage, and macronutrient intakes in postmenopausal Caucasian and Chinese-Canadian women. *Nutrition and Cancer, 63*(5), 687-698.

Tanaka, M., Jaamaa, G., Kaiser, M., Hills, E., Soim, A., Zhu, M., . . . McNutt, L. A. (2007). Racial disparity in hypertensive disorders of pregnancy in New York State: a 10-year longitudinal population-based study. *American Journal of Public Health, 97*(1), 163-170.

Tanentsapf, I., Heitmann, B. L., & Adegboye, A. R. (2011). Systematic review of clinical trials on dietary interventions to prevent excessive weight gain during pregnancy among normal weight, overweight and obese women. *BMC Pregnancy Childbirth, 11*, 81.

Taylor, R. N., Davidge, S. T., & Roberts, J. M. (2009). Endothelial Cell Dysfunction and Oxidative Stress. In M. D. Lindheimer, J. M. Roberts & C. F.G. (Eds.), *Chesley's Hypertensive Disorders in Pregnancy* (3 ed.). USA: Academic Press.

Taylor, R. W., Grant, A. M., Williams, S. M., & Goulding, A. (2010). Sex differences in regional body fat distribution from pre- to postpuberty. *Obesity, 18*(7), 1410-1416.

Than, N. G., Romero, R., Meiri, H., Erez, O., Xu, Y., Tarquini, F., . . . Gonen, R. (2011). PP13, maternal ABO blood groups and the risk assessment of pregnancy complications. *PLoS ONE [Electronic Resource], 6*(7), e21564.

Thangaratinam, S., Rogozinska, E., Jolly, K., Glinkowski, S., Roseboom, T., Tomlinson, J. W., . . . Khan, K. S. (2012). Effects of interventions in pregnancy on maternal weight and obstetric outcomes: meta-analysis of randomised evidence. *BMJ, 344*, e2088.

The Magpie Trial Collaborative Group. (2002). Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial. *The Lancet, 359*(9321), 1877-1890.

The Quit Group and the Ministry of Health. (2009). *Maori Smoking and Tobacco Use 2009*. Wellington: Ministry of Health.

Thomas, J., Paranjothy, S., & Royal College of Obstetricians and Gynaecologists Clinical Effectiveness Support Unit. (2001). *National Sentinel Caesarean Section Audit Report*. RCOG Press: Royal College of Obstetricians and Gynaecologists.

Thompson, J. M., Clark, P. M., Robinson, E., Becroft, D. M., Pattison, N. S., Glavish, N., . . . Mitchell, E. A. (2001). Risk factors for small-for-gestational-age babies: The Auckland Birthweight Collaborative Study. *Journal of Paediatrics & Child Health, 37*(4), 369-375.

Thompson, J. M., Mitchell, E. A., & Borman, B. (1994). Sex specific birthweight percentiles by gestational age for New Zealand. *New Zealand Medical Journal, 107*(970), 1-3.

Tilg, H., & Moschen, A. R. (2006). Adipocytokines: mediators linking adipose tissue, inflammation and immunity. *Nature Reviews. Immunology, 6*(10), 772-783.

Torloni, M. R., Fortunato, S. J., Betran, A. P., Williams, S., Brou, L., Drobek, C. O., . . . Menon, R. (2012). Ethnic disparity in spontaneous preterm birth and maternal pre-pregnancy body mass index. *Archives of Gynecology & Obstetrics, 285*(4), 959-966.

Tschudin, S., Alder, J., Hendriksen, S., Bitzer, J., Popp, K. A., Zanetti, R., . . . Geissbuhler, V. (2009). Previous birth experience and birth anxiety: predictors of caesarean section on demand? *Journal of Psychosomatic Obstetrics & Gynecology, 30*(3), 175-180.

Ujcic-Voortman, J. K., Bos, G., Baan, C. A., Verhoeff, A. P., & Seidell, J. C. (2011). Obesity and body fat distribution: ethnic differences and the role of socio-economic status. *Obesity Facts, 4*(1), 53-60.

University of Otago and Ministry of Health. (2011). *A Focus on Nutrition: Key findings of the 2008/09 New Zealand Adult Nutrition Survey*. Wellington: Ministry of Health.

Vahratian, A., Zhang, J., Hasling, J., Troendle, J. F., Klebanoff, M. A., & Thorp, J. M., Jr. (2004). The effect of early epidural versus early intravenous analgesia use on labor progression: a natural experiment. *American Journal of Obstetrics & Gynecology, 191*(1), 259-265.

Vahratian, A., Zhang, J., Troendle, J. F., Savitz, D. A., & Siega-Riz, A. M. (2004). Maternal prepregnancy overweight and obesity and the pattern of labor progression in term nulliparous women. *Obstetrics & Gynecology, 104*(5 Pt 1), 943-951.

Valensise, H., Vasapollo, B., Gagliardi, G., & Novelli, G. P. (2008). Early and late preeclampsia: two different maternal hemodynamic states in the latent phase of the disease. *Hypertension, 52*(5), 873-880.

Van Gaal, L. F., Mertens, I. L., & De Block, C. E. (2006). Mechanisms linking obesity with cardiovascular disease. *Nature, 444*(7121), 875-880.

van Wassenaer, A. (2005). Neurodevelopmental consequences of being born SGA. *Pediatric Endocrinology Reviews, 2*(3), 372-377.

Vangen, S., Stoltenberg, C., Skrondal, A., Magnus, P., & Stray-Pedersen, B. (2000). Cesarean section among immigrants in Norway. *Acta Obstetricia et Gynecologica Scandinavica, 79*(7), 553-558.

Vangen, S., Stray-Pedersen, B., Skrondal, A., Magnus, P., & Stoltenberg, C. (2003). High risk of cesarean section among ethnic Filipinos: an effect of the paternal contribution to birthweight? *Acta Obstetricia et Gynecologica Scandinavica, 82*(2), 192-193.

Vatten, L. J., & Skjaerven, R. (2004). Is pre-eclampsia more than one disease? *BJOG: An International Journal of Obstetrics & Gynaecology, 111*(4), 298-302.

Veenendaal, M. V. E., van Abeelen, A. F. M., Painter, R. C., van der Post, J. A. M., & Roseboom, T. J. (2011). Consequences of hyperemesis gravidarum for offspring: a systematic review and meta-analysis. *BJOG: An International Journal of Obstetrics & Gynaecology, 118*(11), 1302-1313.

Verdiales, M., Pacheco, C., & Cohen, W. R. (2009). The effect of maternal obesity on the course of labor. *Journal of Perinatal Medicine, 37*(6), 651-655.

Vidarsdottir, H., Geirsson, R. T., Hardardottir, H., Valdimarsdottir, U., & Dagbjartsson, A. (2011). Obstetric and neonatal risks among extremely macrosomic babies and their mothers. *American Journal of Obstetrics & Gynecology, 204*(5), 423.e421-426.

Villar, J., Carroli, G., Zavaleta, N., Donner, A., Wojdyla, D., Faundes, A., . . . Perinatal Health Research, G. (2007). Maternal and neonatal individual risks and benefits associated with caesarean delivery: multicentre prospective study. *BMJ, 335*(7628), 1025.

Villar, J., Valladares, E., Wojdyla, D., Zavaleta, N., Carroli, G., Velazco, A., . . . for the WHO global survey on maternal and perinatal health research group. (2006). Caesarean delivery rates and pregnancy outcomes: the 2005 WHO global survey on maternal and perinatal health in Latin America. *Lancet, 367*(9525), 1819-1829.

Viswanathan, M., Siega-Riz, A., Moos, M.-K., Deierlein, A., Mumford, S., Knaack, J., . . . Lohr, K. (2008). Outcomes of Maternal Weight Gain *Evidence Report/Technology Assessment No.168*. Rockville, MD:Agency for Healthcare Research and Quality: (Prepared by RTI International–University of North Carolina Evidence-based Practice Center under Contract No. 290-02-0016.) AHRQ Publication No. 08-E009.

Volgyi, E., Tylavsky, F. A., Lyytikainen, A., Suominen, H., Alen, M., & Cheng, S. (2008). Assessing body composition with DXA and bioimpedance: effects of obesity, physical activity, and age. *Obesity, 16*(3), 700-705.

Vollebregt, K. C., van der Wal, M. F., Wolf, H., Vrijkotte, T. G., Boer, K., & Bonsel, G. J. (2008). Is psychosocial stress in first ongoing pregnancies associated with pre-eclampsia and gestational hypertension? *BJOG, 115*(5), 607-615.

von Dadelszen, P., Magee, L. A., & Roberts, J. M. (2003). Subclassification of preeclampsia. *Hypertension in Pregnancy, 22*(2), 143-148.

Wagner, M. (2000). Choosing caesarean section. *Lancet, 356*(9242), 1677-1680.

Wallis, A. B., Saftlas, A. F., Hsia, J., & Atrash, H. K. (2008). Secular trends in the rates of preeclampsia, eclampsia, and gestational hypertension, United States, 1987-2004. *American Journal of Hypertension, 21*(5), 521-526.

Walton, A., & Hammond, S. (1938). Maternal effects on growth and conformation in Shire horse-Shetland pony crosses. *Proceedings of the Royal Society of London. Series B: Biological Sciences, 125*(B), 311-335.

Wang, J., Thornton, J. C., Russell, M., Burastero, S., Heymsfield, S., & Pierson, R. N., Jr. (1994). Asians have lower body mass index (BMI) but higher percent body fat than do whites: comparisons of anthropometric measurements. *American Journal of Clinical Nutrition, 60*(1), 23-28.

Wax, J. R., Cartin, A., Pinette, M. G., & Blackstone, J. (2004). Patient Choice Cesarean: An Evidence-Based Review. *Obstetrical and Gynecological Survey, 59*(8), 601-616.

Weiss, J. L., Malone, F. D., Vidaver, J., Ball, R. H., Nyberg, D. A., Comstock, C. H., . . . for the FASTER Consortium. (2004). Threatened abortion: A risk factor for poor pregnancy outcome, a population-based screening study. *American Journal of Obstetrics & Gynecology, 190*(3), 745-750.

Weissgerber, T. L., & Wolfe, L. A. (2006). Physiological adaptation in early human pregnancy: adaptation to balance maternal-fetal demands. *Applied Physiology, Nutrition, & Metabolism = Physiologie Appliquee, Nutrition et Metabolisme, 31*(1), 1-11.

Wells, J. C. (2012). Ethnic variability in adiposity, thrifty phenotypes and cardiometabolic risk: addressing the full range of ethnicity, including those of mixed ethnicity. *Obesity Reviews, 13 Suppl 2*, 14-29.

Wells, J. C. K. (2007). Sexual dimorphism of body composition. *Best Practice & Research Clinical Endocrinology & Metabolism, 21*(3), 415-430.

White, P., Gunston, J., Salmond, C., Atkinson, J., & Crampton, P. (2008). *Atlas of Socioeconomic Deprivation in New Zealand NZDep2006*. Wellington: Ministry of Health.

WHO/IASO/IOTF. (2000). The Asia-Pacific perspective: Redefining Obesity and its Treatment. Melbourne. Retreived from http://www.wpro.who.int/internet/resources.ashx/NUT/Redefining+obesity.pdf

Wikipedia the free encyclopedia. (2012). Disability-adjusted life year. Retrieved 17 August, 2012, from https://en.wikipedia.org/wiki/Disability-adjusted_life_year

Wilcox, M. A., Johnson, I. R., Maynard, P. V., Smith, S. J., & Chilvers, C. E. (1993). The individualised birthweight ratio: a more logical outcome measure of pregnancy than birthweight alone. *British Journal of Obstetrics & Gynaecology, 100*(4), 342-347.

Wilcox, M. A., Newton, C. S., & Johnson, I. R. (1995). Paternal influences on birthweight. *Acta Obstetricia et Gynecologica Scandinavica, 74*(1), 15-18.

Williams, D. (2003). Pregnancy: a stress test for life. *Current Opinion in Obstetrics & Gynecology, 15*(6), 465-471.

Williams, M., Southam, M., & Gardosi, J. (2010). Antenatal detection of fetal growth restriction and stillbirth risk in mothers with high and low body mass index. *Archives of Disease in Childhood Fetal & Neonatal Edition, 95*, Fa92.

Wilson, B. J., Watson, M. S., Prescott, G. J., Sunderland, S., Campbell, D. M., Hannaford, P., & Smith, W. C. (2003). Hypertensive diseases of pregnancy and risk of hypertension and stroke in later life: results from cohort study. *BMJ, 326*(7394), 845.

Wilson, D. M., Bennett, A., Adamson, D. G., Nagashima, R. J., Liu, F., Dentale, M. L., . . . Rosenfeld, R. G. (1982). Somatomedins in Pregnancy: A Cross-Sectional Study of Insulin-Like Growth Factors I and II and Somatomedin Peptide Content in Normal Human Pregnancies. *Journal of Clinical Endocrinology & Metabolism, 55*(5), 858-861.

Wilson, M. J. A., Morganti, A. A., Zervoudakis, I., Letcher, R. L., Romney, B. M., Von Oeyon, P., . . . Laragh, J. H. (1980). Blood pressure, the renin-aldosterone system and sex steroids throughout normal pregnancy. *The American Journal of Medicine, 68*(1), 97-104.

Wilson, P. W., Abbott, R. D., & Castelli, W. P. (1988). High density lipoprotein cholesterol and mortality. The Framingham Heart Study. *Arteriosclerosis, 8*(6), 737-741.

Wimalasundera, R. C., Larbalestier, N., Smith, J. H., de Ruiter, A., Mc, G. T. S. A., Hughes, A. D., . . . Taylor, G. P. (2002). Pre-eclampsia, antiretroviral therapy, and immune reconstitution. *Lancet, 360*(9340), 1152-1154.

Winkleby, M. A., Kraemer, H. C., Ahn, D. K., & Varady, A. N. (1998). Ethnic and socioeconomic differences in cardiovascular disease risk factors: findings for women from the Third National Health and Nutrition Examination Survey, 1988-1994. *JAMA, 280*(4), 356-362.

Wiznitzer, A., Mayer, A., Novack, V., Sheiner, E., Gilutz, H., Malhotra, A., & Novack, L. (2009). Association of lipid levels during gestation with preeclampsia and gestational diabetes mellitus: a population-based study. *American Journal of Obstetrics & Gynecology, 201*(5), 482.e481-488.

Wiznitzer, A., Reece, E. A., Homko, C., Furman, B., Mazor, M., & Levy, J. (1998). Insulin-like growth factors, their binding proteins, and fetal macrosomia in offspring of nondiabetic pregnant women. *American Journal of Perinatology, 15*(1), 23-28.

Wolfe, K. B., Rossi, R. A., & Warshak, C. R. (2011). The effect of maternal obesity on the rate of failed induction of labor. *American Journal of Obstetrics & Gynecology, 205*(2), 128.e121-127.

Woods, K. A., Camacho-Hubner, C., Savage, M. O., & Clark, A. J. (1996). Intrauterine growth retardation and postnatal growth failure associated with deletion of the insulin-like growth factor I gene. *New England Journal of Medicine, 335*(18), 1363-1367.

World Health Organization. (2000). *Obesity: Preventing and Managing the Global Epidemic: report of a WHO Consultation* (WHO Technical Report Series 894). Geneva, Switzerland: World Health Organisation.

World Health Organization. (2011). World health statistics 2011. Switzerland: WHO Press.

World Health Organization. (2012a). Global Health Observatory (GHO). Obesity Situation and trends. Retrieved from http://www.who.int/gho/ncd/risk_factors/obesity_text/en/index.html

World Health Organization. (2012b). Metrics: Disability-Adjusted Life Year (DALY). *Health statistics and health information systems*. Retrieved from http://www.who.int/healthinfo/global_burden_disease/metrics_daly/en/index.html

World Health Organization. (2012c, May 2012). Obesity and overweight. Fact sheet N°311. Retrieved from http://www.who.int/mediacentre/factsheets/fs311/en/index.html

World Health Organization expert consultation. (2004). Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet, 363*(9403), 157-163.

Wurtman, R. J., & Wurtman, J. J. (1995). Brain serotonin, carbohydrate-craving, obesity and depression. *Obes Res, 3 Suppl 4*, 477S-480S.

Xiong, X., Demianczuk, N. N., Saunders, L. D., Wang, F. L., & Fraser, W. D. (2002). Impact of preeclampsia and gestational hypertension on birth weight by gestational age. *American Journal of Epidemiology, 155*(3), 203-209.

Yasmeen, S., Wilkins, E. E., Field, N. T., Sheikh, R. A., & Gilbert, W. M. (2001). Pregnancy outcomes in women with systemic lupus erythematosus. *Journal of Maternal-Fetal Medicine, 10*(2), 91-96.

Yogev, Y., Ben-Haroush, A., Chen, R., Rosenn, B., Hod, M., & Langer, O. (2004). Diurnal glycemic profile in obese and normal weight nondiabetic pregnant women. *American Journal of Obstetrics & Gynecology, 191*(3), 949-953.

Yu, V. Y., & Upadhyay, A. (2004). Neonatal management of the growth-restricted infant. *Seminars in Fetal and Neonatal Medicine, 9*(5), 403-409.

Zavalza-Gomez, A. B. (2011). Obesity and oxidative stress: a direct link to preeclampsia? *Archives of Gynecology & Obstetrics, 283*(3), 415-422.

Zeitlin, J., Ancel, P. Y., Saurel-Cubizolles, M. J., & Papiernik, E. (2000). The relationship between intrauterine growth restriction and preterm delivery: an empirical approach using data from a European case-control study. *BJOG, 107*(6), 750-758.

Zetterstrom, K., Lindeberg, S. N., Haglund, B., & Hanson, U. (2006). Chronic hypertension as a risk factor for offspring to be born small for gestational age. *Acta Obstetricia et Gynecologica Scandinavica, 85*(9), 1046-1050.

Zhang, J., & Bowes, W. A., Jr. (1995). Birth-weight-for-gestational-age patterns by race, sex, and parity in the United States population. *Obstetrics & Gynecology, 86*(2), 200-208.

Zhang, J., Bricker, L., Wray, S., & Quenby, S. (2007). Poor uterine contractility in obese women. *BJOG: An International Journal of Obstetrics & Gynaecology, 114*(3), 343-348.

Zhang, J., Kendrick, A., Quenby, S., & Wray, S. (2007). Contractility and calcium signaling of human myometrium are profoundly affected by cholesterol manipulation: implications for labor? *Reproductive Sciences, 14*(5), 456-466.

Zhang, J., Merialdi, M., Platt, L. D., & Kramer, M. S. (2010). Defining normal and abnormal fetal growth: promises and challenges. *American Journal of Obstetrics and Gynecology, 202*(6), 522-528.

Zhang, J., Mikolajczyk, R., Grewal, J., Neta, G., & Klebanoff, M. (2011). Prenatal application of the individualized fetal growth reference. *American Journal of Epidemiology, 173*(5), 539-543.

Zhang, X., Cnattingius, S., Platt, R. W., Joseph, K. S., & Kramer, M. S. (2007). Are babies born to short, primiparous, or thin mothers "normally" or "abnormally" small? *Journal of Pediatrics, 150*(6), 603-607, 607.e601-603.

Zhang, X., Platt, R. W., Cnattingius, S., Joseph, K. S., & Kramer, M. S. (2007). The use of customised versus population-based birthweight standards in predicting perinatal mortality. *BJOG: An International Journal Of Obstetrics And Gynaecology, 114*(4), 474-477.

Zhang, Y., Proenca, R., Maffei, M., Barone, M., Leopold, L., & Friedman, J. M. (1994). Positional cloning of the mouse obese gene and its human homologue. *Nature, 372*(6505), 425-432.

Zhong, Y., Tuuli, M., & Odibo, A. O. (2010). First-trimester assessment of placenta function and the prediction of preeclampsia and intrauterine growth restriction. *Prenatal Diagnosis, 30*(4), 293-308.

Zhu, J. L., Obel, C., Hammer Bech, B., Olsen, J., & Basso, O. (2007). Infertility, infertility treatment, and fetal growth restriction. *Obstetrics & Gynecology, 110*(6), 1326-1334.

Zhu, S., Wang, Z., Heshka, S., Heo, M., Faith, M. S., & Heymsfield, S. B. (2002). Waist circumference and obesity-associated risk factors among whites in the third National Health and Nutrition Examination Survey: clinical action thresholds. *American Journal of Clinical Nutrition, 76*(4), 743-749.