Maternal health after having survived a potentially life-threatening complication in pregnancy

by

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Supervisor: Prof RC Pattinson

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DECLARATION

I, Priya Soma-Pillay hereby declare that the dissertation I submit to the University of Pretoria for my PhD degree in Obstetrics and Gynaecology is my own work and has not been submitted to any other facility prior.

_____

Priya Soma-Pillay

30th day of August 2017

DEDICATION

To all the women who consented to participate in this study and to all women globally who suffer pregnancy complications.

ACKNOWLEDGEMENTS

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To my mother, Ruxmani Soma, who has always encouraged her children to have a good work ethic.

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ETHICAL APPROVAL

The Research Ethics Committee, Faculty Health Sciences, University of Pretoria complies with ICH-GCP guidelines and has US Federal wide Assurance.
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Faculty of Health Sciences Research Ethics Committee

10/05/2013

Approval Notice
New Application

Ethics Reference No.: 125/2013

Title: Maternal health after having survived a potentially life-threatening complication in pregnancy

Dear Dr P Soma-Pillay

The **New Application** for your research received in March 2013, was approved by the Faculty of Health Sciences Research Ethics Committee on the 10/05/2013.

Please note the following about your ethics approval:
- Ethics Approval is valid for 5 years.
- Please remember to use your protocol number (125/2013) on any documents or correspondence with the Research Ethics Committee regarding your research.
- Please note that the Research Ethics Committee may ask further questions, seek additional information, require further modification, or monitor the conduct of your research.

Ethics approval is subject to the following:
Standard Conditions:
- The ethics approval is conditional on the receipt of 6 monthly written Progress Reports, and
- The ethics approval is conditional on the research being conducted as stipulated by the details of all documents submitted to the Committee. In the event that a further need arises to change who the investigators are, the methods or any other aspect, such changes must be submitted as an Amendment for approval by the Committee.

The Faculty of Health Sciences Research Ethics Committee complies with the SA National Act 61 of 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 and 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes 2004 (Department of Health).

We wish you the best with your research.

Yours sincerely

DR R SOMMERS; MBChB; MMed(Int); MPharmMed.
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SUMMARY

OBJECTIVES

Maternal near-miss audits were initially introduced to evaluate the quality of obstetric care at the time of the event. One of the principle advantages of studying near-misses is that these women are able to adequately report the obstacles and delays they face to assure their continued survival. The primary objective of the study was to compare the long-term health of women who suffered a serious acute morbidity event in pregnancy to a control group of low risk women who have had a normal pregnancy outcome. We wanted to determine whether the insult associated with maternal near-misses makes women more vulnerable to further organ dysfunction. The secondary aim was to determine the spectrum of morbidity in the Pretoria Academic Complex (PAC) and the barriers to obstetric care.

METHODS AND MATERIALS

This study consists of 6 sub-studies to address the research problem. The first study investigated the epidemiology of the spectrum of morbidity in the PAC. Delivery data related to demographic and reproductive characteristics, pregnancy and childbirth complications were collected on a daily basis from hospitals in the PAC: Steve Biko Academic Hospital, Kalafong Provincial Tertiary Hospital, Tshwane District Hospital, Pretoria West and Mamelodi Hospitals and from Stanza Bopape and Eersterust Midwife Obstetric Units. Daily audit meetings were held at the 2 tertiary hospitals to identify women with potentially life-threatening conditions. We further investigated the delays/barriers in providing obstetric care to women who were classified as a maternal near miss. The “three delays model” was used to identify the phases of delay in the health system. Three studies investigated the long-term complications in women with severe pre-eclampsia in pregnancy. Magnetic resonance imaging, echocardiography, and digital photos of the eye were taken at delivery and 1-year post-partum. In the last study, we compared the quality of life of women classified as a maternal near miss to a group of women

with an uncomplicated low-risk pregnancy using the World Health Organisation Quality of Life questionnaire.

RESULTS

About one in 20 pregnant women in the PAC had a potentially life-threatening condition and 0.5% a life-threatening condition in pregnancy. One or more factors causing a delay in accessing care were identified in 83% of near-miss cases. Near miss women have a poorer quality of life 1-year after delivery than women with uncomplicated pregnancies. Severe pre-eclampsia in pregnancy was found to have the following long-term effects on maternal health:

- Cerebral white matter lesions were demonstrated in 48% of women with severe pre-eclampsia at 1 year postpartum
- Women with early onset pre-eclampsia requiring delivery prior to 34 weeks had an increased risk of cardiac diastolic dysfunction
- Retinal artery and venular calibers in women with pre-eclampsia are smaller than those of normotensive women at 1-year postpartum

CONCLUSION

Women who experience a severe acute morbidity event in pregnancy must be recognised as a vulnerable group who are require increased postpartum care and surveillance. Ideally all tertiary centres should have near-miss clinics for post-partum care. Any risk factors for future disease should be identified and modified to promote long-term health.

Keywords

Maternal near-miss, pre-eclampsia, cerebral white matter lesion, cardiac diastolic dysfunction

LIST OF ABBREVIATIONS

AIDS – Acquired immune deficiency syndrome

BMI – Body mass index

BNP – Brain naturetic peptide

CHC – Community health centre

CRAE – Central retinal arteriolar equivalent

CRVE - Central retinal venular equivalent

cCRAE – corrected central retinal arteriolar equivalent

cCRVE – corrected central retinal venular equivalent

CT – Computerised axial tomography

DT – Deceleration time

E /A ratio – Mitral E-wave and mitral A-wave velocity ratio

HELLP – Haemolysis, elevated liver enzymes, low platelets

HIV – Human immunodeficiency virus

ICU – Intensive Care Unit

iMMR – institutional Maternal Mortality Ratio

ISSHP – International Society for the Study of Hypertension in Pregnancy

KAH – Kalafong Provincial Tertiary Hospital

LA – Left atrial

LAP – Left atrial pressure

LV – Left ventricular

LVEF – Left ventricular ejection fraction

MI – Mortality index

MOU – Midwife Obstetric Unit

MNM IR – Maternal near miss incidence ratio

MRI – Magnetic resonance imaging

PAC - Pretoria Academic Complex

PLGF – Placental growth factor

PNMR - Perinatal mortality rate

PRES – Posterior reverse encephalopathy syndrome

QoL – Quality of Life

SBAH – Steve Biko Academic Hospital

SD – standard deviation

sFLT-1 – Tyrosine kinase receptor-1

SMO – Severe maternal outcome

SMOR – Severe maternal outcome ratio

TB - Tuberculosis

TDH – Tshwane District Hospital

VEGF – Vascular endothelial growth factor

WHO – World Health Organisation

WHOMCS – WHO Global survey

WHOQOL – WHO quality of life

WMLs – White matter lesions

INTRODUCTION TO THE STUDY

The introduction focuses on the background to the study and the rationale for the research. This chapter describes the research problem and the aims and objectives of this thesis. The thesis consists of six research papers and a concluding chapter.

Background

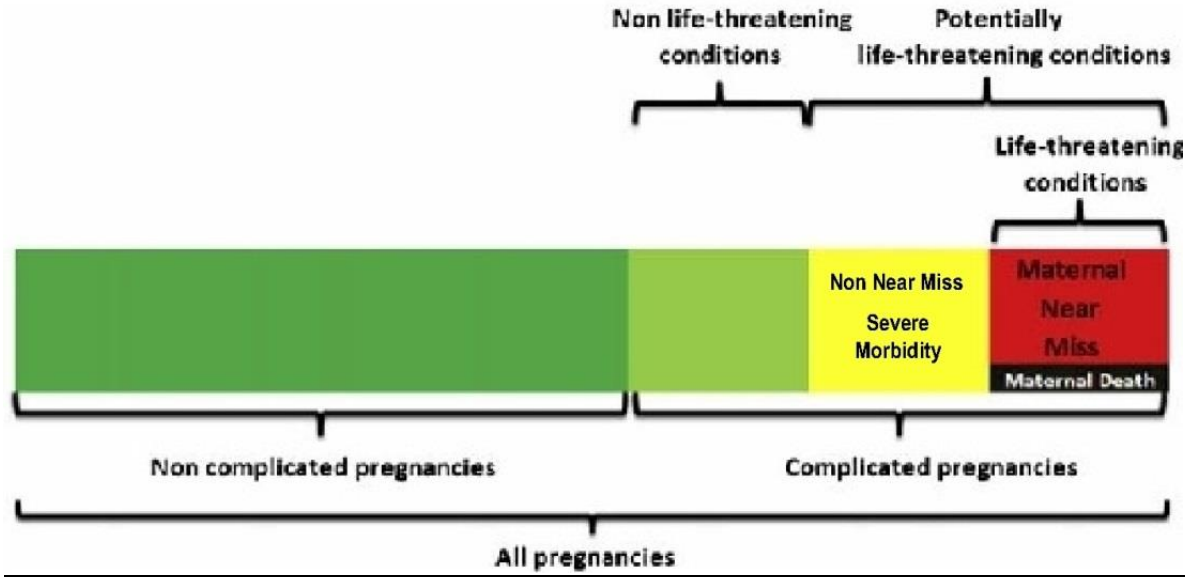
A maternal near miss refers to a woman who nearly died but survived a complication that occurred during pregnancy, childbirth or within 42 days of pregnancy.[1] Approximately 20 million acute complications of pregnancy occur globally every year.[2] Improvement in healthcare means that increasing numbers of women are surviving acute morbidity events but the long-term repercussions of these events have not been evaluated fully. There is some evidence suggesting that maternal ill health continues beyond the immediate post-partum period and might affect women's lives. A study in Burkino Faso has shown that women with severe obstetric complications, and their babies were significantly more likely to die after discharge compared with women with an uncomplicated delivery.[3] Women with severe obstetric complications are also more likely to experience depression, anxiety and suicidal thoughts.[3]

Other investigators have evaluated the repercussions of severe biological or traumatic events and have reported that survivors are at an increased risk of death in the five years after the event.[4] After release from hospital, these patients continue to develop both organic and emotional problems, including cardiac, respiratory and neurological complications.[5]One of the principle advantages of studying near-misses, is the possibility of hearing the experience of women directly. These women are believed to be able to adequately report the obstacles and delays they face to assure their continued survivial.[6]

Pregnancy can be looked at as a "stress test." During this period certain organ systems become vulnerable to dysfunction or failure. It is important to find the correct balance between maternal well-being and optimal timing of delivery of the neonate. Prolonging a pregnancy as a result of excessive concern for the neonate can be detrimental to maternal health.

Although a maternal near miss case can only be identified retrospectively, it is clinically useful to prospectively identify women with potentially life-threatening conditions. A woman who develops a life-threatening condition is either a maternal near miss or a maternal death. According to the Saving Mothers Report, 26.7% of maternal deaths in South Africa during 2011-2013 were probably avoidable and a further 32.8% were considered possibly avoidable.[7] Obstetric emergencies may occur in women with known risk factors however a significant proportion of serious complications in pregnancy occur in women with no identifiable risk factors. Several factors may influence a woman's ability to access appropriate obstetric care. Evaluating circumstances around near-miss cases have the advantage over maternal death cases because near-miss patients are able to provide direct information after an event. Say et al have described the spectrum of morbidity from an uncomplicated pregnancy to further progression to maternal death.[8] (Figure 1)

Figure 1 – The spectrum of morbidity: from uncomplicated pregnancies to maternal death



From Say L et al. Best practice & Research Clinical Obstetrics and Gynae 2009

There were 41 687 births in the Pretoria Academic Complex between January 2008-December 2009.[9]The maternal near miss incidence ratio (MNM IR) (number of maternal near miss cases per 1000 live births [MNM IR=MNM/LB]) for this period was 8.99 per 1000 births. The most common causes of severe morbidity during this period was, obstetric haemorrhage, hypertension, pre-existing medical and surgical conditions and complications associated with miscarriage. There were more women with life-threatening conditions associated with pre-existing medical and surgical conditions and complications of hypertension in 2008-2009 than during the periods 1997-1998 and 2002-2004.

In the WHO Global survey, (WHOMCS 2012) postpartum haemorrhage and pre-eclampsia/eclampsia were the most frequent obstetric complications found among women with severe maternal outcomes (26.7% and 25.9% respectively).[10] Intensive care-unit admission, hysterectomy, blood transfusion, cardiac or renal complications and eclampsia were the most important indicators of severe

maternal morbidity according to the WHO global survey on maternal and perinatal health.[10]

Pre-eclampsia has remained a major cause of maternal morbidity and mortality in South Africa for more than a decade. Physiological changes that take place in an uncomplicated pregnancy include: insulin resistance, hyperlipidaemia, hypercoagulability, inflammation and a hyperdynamic circulation.[11] These changes are exaggerated in women with pre-eclampsia. Some of the physiological changes associated with pre-eclampsia are also risk factors for the metabolic syndrome and future cardiovascular disease. Additionally impaired endothelial function during pre-eclampsia increases the risk for cerebral oedema and vascular damage. It was previously believed that complications associated with pre-eclampsia end with the delivery of the fetus and placenta. It is now well established that pre-eclampsia is a risk factor for future hypertension, diabetes, ischemic heart disease and venous thromboembolism. The effect of pre-eclampsia on individual organ function in an African population is not known.

Women who experience severe morbidity in pregnancy are more likely have an infant with a low or very low birth weight, stillbirth, early neonatal death, admission to the neonatal ICU, a prolonged maternal postpartum hospital stay and caesarean section.[12] Mothers of preterm infants have a lower quality of life (QOL) experience compared to mothers of near-term and term infants.[13] This difference is most likely related to both the effects of morbidity of the mother and the medical condition of the preterm infant.[13] The fear of infant death, travel to and from hospital, prolonged and expensive hospitalisation with major disruption to family routines can lead to psychological turmoil.[14] Mothers of preterm infants have higher psychological distress and depression.[15,16] The World Health Organisation defines QoL as an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns.[17] Quality of life is a broad ranging concept affected in a complex way by the person's physical health, psychological state,

level of dependence, social relationship to salient features of their environment. Several studies have documented the effect of depressive symptoms on the quality of life of women after pregnancy, however little is known of the impact of severe morbidity on maternal functioning and well-being.[18]

Motivation for the study

It is unknown whether continuing a pregnancy in a patient with severe organ dysfunction does long-term harm to maternal health. The extent of this "harm" is also unknown. We are also uncertain whether this organ dysfunction is a continuum and progressively becomes worse or whether there is a "critical level" of organ dysfunction which in the long-term leads to organ failure. This study aims to describe the long term outcome of pregnant women with life threatening conditions and to start addressing the question whether pregnant women with potentially life threatening conditions should be delivered earlier to protect them from long term maternal ill-health.

Research Problem

The primary aim of this study was to investigate the long-term organ system function in a group of women who have suffered severe morbidity in pregnancy and further compare this group to a control group of low-risk women who have had a normal pregnancy outcome. We also investigated whether the insult associated with severe morbidity in pregnancy predisposed this group of vulnerable women to further long-term organ dysfunction.

The thesis consists of six studies:

1. Maternal near miss and maternal death in the Pretoria Academic Complex, South Africa: a population – based study
2. Barriers to obstetric care among maternal near misses
3. Cerebral white matter lesions after pre-eclampsia
4. Cardiac diastolic function after recovery from pre-eclampsia
5. Changes in retinal microvascular caliber after pregnancies complicated by pre-eclampsia
6. Quality of life one year after a severe acute morbidity event during pregnancy.

Although important cases of renal, respiratory and liver failure were identified during the study, these cases were too few to be able to study over of the PhD

Aims and objectives

Chapter 1 – Determine the spectrum of severe maternal morbidity and mortality in the Pretoria Academic Complex and compare the data with previous surveys and the World Health Organisation (WHO) Multicountry Survey on Maternal and Newborn Health. The WHO study was used as a comparison because it is the only study to characterise maternal morbidity occurring in a worldwide network of health facilities. This study also gives the magnitude of the of the problem and what resources will be required to manage these women further.

Chapter 2 – Determine the reasons for delay in accessing appropriate obstetric care for women who were classified as maternal near-misses.

Chapter 3 – Assess the presence and severity of cerebral white matter lesions amongst pre-eclamptic women at delivery, 6 months and 1 year postpartum and determine the possible pathophysiology and associated risk factors.

Chapter 4 – Determine the cardiac diastolic function at delivery and 1 year postpartum in women with severe pre-eclampsia and compare with a control group

of low risk women. The secondary aim is to determine possible future cardiovascular risk in women with severe pre-eclampsia.

Chapter 5 – Compare the retinal microvascular caliber at delivery and 1-year postpartum in women with severe pre-eclampsia and a control group of low risk women who were normotensive during pregnancy.

Chapter 6 – Compare the quality of life at 1-year among pregnant women who were classified as a maternal near miss to a control group of women who experienced an uncomplicated low risk pregnancy.

General hypothesis

Women who have a potentially life-threatening complication in pregnancy have a greater risk of long-term morbidity and mortality than women who experience a normal uncomplicated pregnancy

General methods

This study was a hospital-based follow-up of a cohort of women with potentially life-threatening conditions. The cohort of women with a potentially life-threatening condition was compared to a group of women who experienced an uncomplicated low-risk pregnancy

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CHAPTER 1

Maternal near miss and maternal death in the Pretoria Academic Complex, South Africa: A population-based study

Aims and objectives
To determine the spectrum of maternal morbidity and mortality in the Pretoria Academic Complex.

Methods
A descriptive population-based study which included all women delivering at the Pretoria Academic Complex (PAC). The definition, criteria and indicators of the WHO near miss and maternal death were used to identify women with severe complications in pregnancy.

Results
Between 1 August 2013 and 31 July 2014 there were 26 614 deliveries in the PAC. The institutional maternal mortality ratio (iMMR) was 71.4/100 000 live births. The HIV-infection rate was 19.9% and 2.7% of women had an unknown HIV status. One thousand one hundred and twenty women (4.21%) developed potentially life threatening conditions (PLTC) and 136 (0.51%) women developed life-threatening conditions. The overall mortality index was 14.0%, for non-pregnancy related infections 30.0%, obstetric haemorrhage 2.0% and hypertension 13.6%. Forty-percent of the women with life-threatening conditions were referred from the primary level of care. Vascular, uterine and coagulation dysfunction were the most frequent organ dysfunctions in women with life-threatening conditions. The overall perinatal mortality rate was 26.94/1000 births; 23.1/1000 for women with non-life threatening conditions and 198.0/1000 for women with life-threatening conditions.

Conclusion
Almost 5% of pregnant women in the PAC had potentially life-threatening conditions. Forty percent of women presented with an acute emergency to a primary level facility and had to be transferred for tertiary care. All health care professionals involved in maternity care must have knowledge and skills in managing obstetric emergencies. Review of the basic antenatal care protocol is necessary.

1.1 INTRODUCTION

There were 4 452 maternal deaths in South Africa for the period 2011-2013.[1] There has been a decrease in the institutional maternal mortality ratio (iMMR) in South Africa for the period 2011-2013 compared to the 2008- 2010 triennium, however further work needs to be done to meet the fifth Millennium Development Goal. In order to reduce maternal mortality, it is important to understand the process of obstetric care, identify weaknesses within the system and finally implement interventions for improving care.[2]

A woman who experiences and survives a severe health condition during pregnancy, childbirth or postpartum is classified as a maternal near miss.[3] By studying cases of maternal deaths and near misses important information can be obtained about the processes that take place within health care systems responsible for the care of pregnant women. Near miss cases share many pathological and circumstantial characteristics with maternal deaths; however near miss cases have the advantage of providing additional information about obstacles that have to be overcome after the onset of an acute complication. Although a maternal near miss case can only be identified retrospectively, it is clinically useful to prospectively identify women with potentially life-threatening conditions. A woman who develops a life-threatening condition will either become a maternal near miss case or maternal death.

The purpose of this study was to determine the spectrum of severe maternal morbidity and mortality in the Pretoria Academic Complex and compare the data with previous surveys and the World Health Organisation (WHO) Multicountry Survey on Maternal and Newborn Health.[4]

1.2 METHODS

This was a descriptive population-based study which took place from 1 August 2013 to 31 July 2014 at 9 delivery facilities in central, south-western and eastern Tshwane. The following delivery units were included in the study: Steve Biko Academic Hospital (SBAH) (level 3), Kalafong Hospital (KAH) (level 3), Mamelodi Hospital (level 2), Tshwane District Hospital (level 1), Pretoria West Hospital (level 1), Laudium Community Health centre (CHC) with Midwife Obstetric Unit (MOU), (CHC), Eersterust MOU (CHC), Stanza Bopape and Dark City Clinics (CHC). The Steve Biko and Kalafong Hospitals are tertiary referral hospitals which receive referrals from outside the Gauteng province. The data was only analysed for women living in the Tshwane region; those living outside our complex were excluded. Cases of abortions and ectopic pregnancy were excluded from the study. Delivery data was recorded on a daily basis at all the health facilities and daily audit meetings were held at SBAH and KAH to identify women with life-threatening conditions and organ dysfunction in pregnancy. The following World Health Organisation (WHO) indicators were used to quantify women with severe complications in pregnancy[2,5]:

Maternal near miss – a woman who nearly died but survived a complication that occurred during pregnancy, childbirth or within 42 days of termination of pregnancy. The WHO near miss criteria are listed in table 1.

Maternal death – A maternal death is the death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and the site of pregnancy from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes.

Life-threatening conditions/severe maternal outcome (SMO) – refers to all women who either qualified as having maternal near miss or who died. It is the sum of maternal near misses and maternal deaths.

Potentially life-threatening condition – the 5 described by the WHO are: severe postpartum haemorrhage, severe pre-eclampsia, eclampsia, sepsis/severe systemic infection and ruptured uterus. The operational definitions of the 5 potentially life-threatening conditions are:

- Severe postpartum haemorrhage – genital bleeding after delivery, with at least one of the following: perceived abnormal bleeding (1000ml or more) or any bleeding with hypotension or blood transfusion

- Severe pre-eclampsia – persistent systolic blood pressure of 160mmHg or more or a diastolic blood pressure of 110mmHg; proteinuria of 5g or more in 24 hours; oliguria of < 400ml in 24 hours; and HELLP syndrome or pulmonary oedema. Excludes eclampsia.

- Eclampsia – generalised fits in a patient without previous history of epilepsy. Includes coma in pre-eclampsia.

- Severe sepsis/ systemic infection – presence of fever (body temperature > 38^0C), a confirmed or suspected infection (eg chorioamnionitis, septic abortion, endometritis, pneumonia), and at least one of the following: heart rate > 90, respiratory rate > 20, leukopenia (white blood cells < 4000), leucocytosis (white blood cells > 12 000).

- Uterine rupture – rupture of uterus during labour confirmed by laparotomy.

Severe Maternal Outcome Ratio (SMOR) – refers to the number of women with life-threatening conditions per 1000 live births. This indicator gives an estimation of the amount of care that would be needed in an area.

Mortality index – the number of maternal deaths divided by the number of women with life-threatening conditions, expressed as a percentage.

1.2.1 Table 1. The WHO near miss criteria

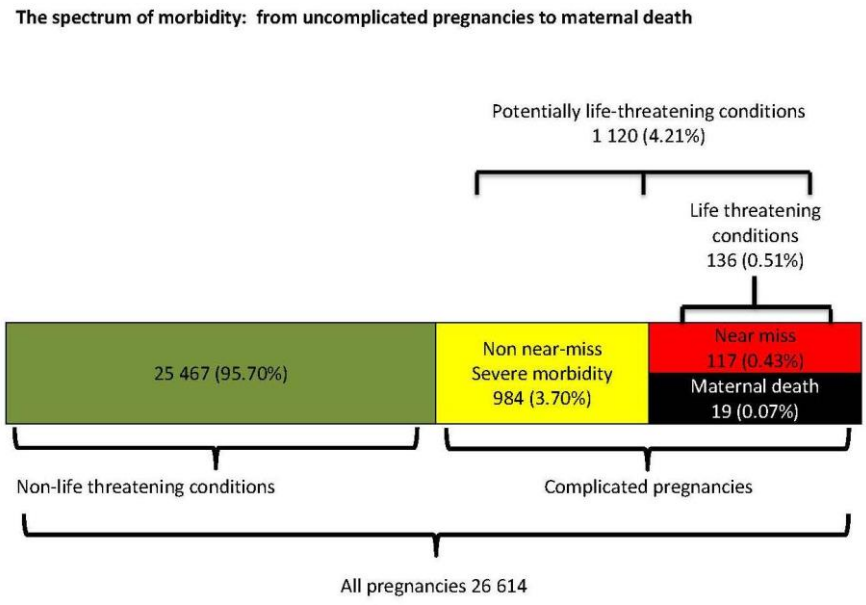
Clinical criteria	
Acute cyanosis	Breathing rate > 40 < 6/min
Oliguria unresponsive to fluids or diuretics	Loss of consciousness, no pulse/heartbeat
Jaundice concomitantly with pre-eclampsia	Gasping
Shock	Coagulation disorders
Cerebrovascular accident	Total paralysis
Laboratory criteria	
Oxygen saturation < 90% for > 60 minutes	Acute thrombocytopenia (< 50 000 platelets)
Creatinine > 300umol/l or > 3.5mg/dl	Bilirubin > 100umol/l or > 6.0mg/dl
Unconscious, presence of glucose and ketoacidosis in urine	Lactate > 5
PaO2/FiO2<200mmHg	pH < 7.1
Management criteria	
Use of continuous vasoactive drug	Dialysis for treatment of acute kidney failure
Puerperal hysterectomy due to infection or haemorrhage	Cardiopulmonary resuscitation
Transfusion > 5 units of red cell concentrate	Intubation and ventilation for a period > 60 minutes, unrelated to anaesthesia

Descriptive statistics in the form of means and standard deviations in the case of continuous data and frequencies and percentages in the case of categorical data was calculated. Ethical approval was obtained from the University of Pretoria Ethics committee (no: 125/2013).

1.3 RESULTS

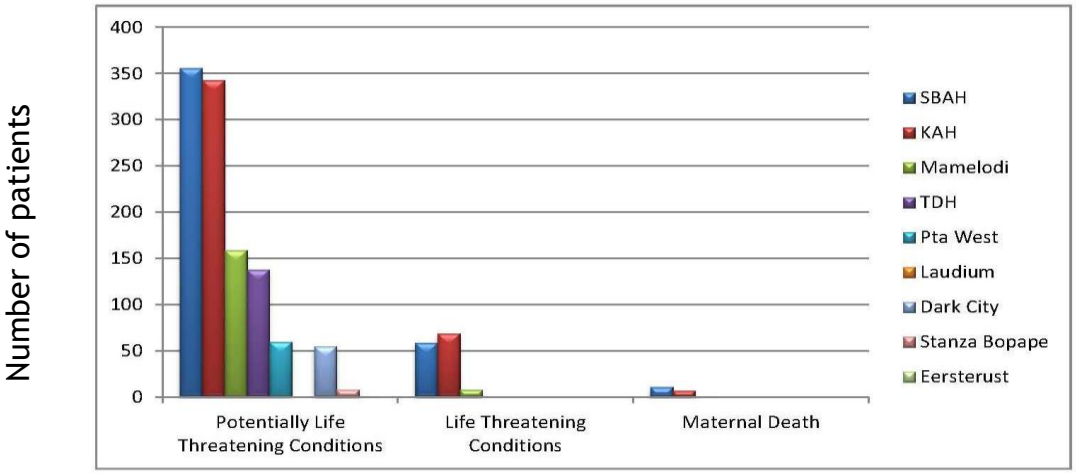
There were 26 614 deliveries in the Pretoria Academic Complex during the study period. One-hundred and thirty six women developed life-threatening conditions and there were 19 maternal deaths. The severe maternal outcome ratio (SMOR) was 5.1/1000 births and the mortality index was 14.0%. The overall caesarean section rate was 25.2% and that for women with life-threatening conditions 61.02%. The HIV infection rate for the general population was 19.9%, 23.1% for near-misses and 36.8% for mothers who died. The HIV-disease status was unknown in 2.7% of patients. The spectrum of morbidity from uncomplicated pregnancies to maternal death is illustrated in figure 1.

1.3.1 Figure 1 The spectrum of morbidity: from uncomplicated pregnancies to maternal death



Most of the patients with potentially life threatening conditions and life threatening conditions were treated at the two tertiary level hospitals. Forty-six (39.3%) women who were classified as near misses and 7 (36.8%) women who demised had to be transferred to the two tertiary level hospitals after initially presenting at a lower level of care. The most frequent indications for emergency transfer of women with life-threatening conditions to the tertiary hospitals were: severe preeclampsia (15.4%, n=21), obstetric haemorrhage (13.2% n=18) and organ dysfunction in women with underlying medical disease (6.6%, n=9) (Table 2). The mortality index for SBAH was 18.6%, 10.2% for KAH and 12.5% for Mamelodi Hospital. The distribution of patients with potentially life-threatening conditions in relation to the different levels of care is shown in figure 2.

1.3.2 Figure 2. Distribution of potentially life-threatening conditions, near misses and maternal deaths for the different levels of care



1.3.3 Table 2 Acute life-threatening conditions requiring tertiary care

	Patients referred to tertiary centre from lower levels of care		Patients already in tertiary care	
	n	%	n	%
Obstetric haemorrhage	18	13.2	26	19,1
Pre-eclampsia	21	15.4	22	16.2
Sepsis	3	2.2	11	8.1
Medical/surgical disorders	9	6.6	9	6.6
Non-pregnancy related infections	3	2.2	8	5.9
Anaesthetic disorders	0	0	4	2.9
Other			2	1.5
Total	54	39.7	82	60.3

The frequency of potentially life-threatening disorders is shown in table 3. (Ante-partum haemorrhage and non-pregnancy related infections which are not part of the WHO definition for potentially life-threatening conditions have been included.)

1.3.4 Table 3 Frequency of potentially life-threatening disorders

	All women (n=26 614)	Women with SMO (n=136)	HIV infection in women with SMO (%)
Severe haemorrhage	**660 (2.5%)**	**51 (37.5%)**	**7 (13.7%)**
Ante-partum haemorrhage	301 (1.1%)	17 (12.5%)	1 (5.9%)
Postpartum haemorrhage	336 (1.3%)	31 (22.7%)	4 (12.9%)
Ruptured uterus	23 (0.1%)	3 (2.2%)	2 (66.7%)
Severe hypertensive disorders	**682 (2.6%)**	**44 (32.4%)**	**4 (9.1%)**
Preeclampsia	457 (1.7%)	40 (29.4%)	4 (10.0%)
Eclampsia	225 (0.8%)	4 (2.9%)	0
Other complications			
Puerperal sepsis	35 (0.1%)	14 (10.3%)	2 (14.3%)
Non-pregnancy related infections		20 (14.7%)	20 (100%)

The mortality index for non-pregnancy related infections was 30.0%, obstetric haemorrhage 2.0%, 13.6% for hypertension and 19.0% for medical and surgical disorders (Table 4)

1.3.5 Table 4 Mortality index for different disease conditions

Underlying condition	**Maternal near miss (n)**	**Maternal Death (n)**	**Mortality Index (%)**
Obstetric haemorrhage	**50**	**1**	**2.0%**
Ante-partum haemorrhage	17	0	0
Ruptured uterus	3	0	0
Post-partum haemmorrhage	30	1	3.2%
Hypertension	**38**	**6**	**13.6%**
Chronic	1	0	0
Preeclampsia	35	4	10.0%
Eclampsia	2	2	50.0%
Puerperal sepsis	14	0	0
Non-pregnancy related infections	14	6	**30.0%**
Medical/surgical disorders	17	4	**19.0%**

The near-miss markers and distribution of organ dysfunction are shown in Tables 5 and 6. There were 6 maternal deaths related to HIV and AIDS. Four patients had respiratory failure secondary to TB pneumonia, one patient had bacterial meningitis and one patient demised after presenting with multi-organ failure and milliary tuberculosis. Six mothers demised after having complications related to pre-eclampsia. One patient had a liver rupture, 2 patients had intra-cranial bleeds, 2 patients had respiratory failure due to pulmonary oedema and one patient had a cardiac arrest. The patient who demised as a result of postpartum haemorrhage had a placenta praevia and 2 previous caesarean sections. Although the patient had an ante-natal ultrasound confirming placental location, the diagnosis of placenta accreta was missed. Surgeons encountered a major bleed at caesarean section and

the patient also had 2 re-look laparotomies but the bleeding could not be controlled. Four patients died due to underlying medical disease; one each due to breast cancer, acute on chronic pancreatitis, an anaesthetic complication in a diabetic patient and one patient with a prosthetic heart valve in pregnancy.

There were no maternal deaths at the level 1 hospitals or community health centres and just 1 death at a level 2 hospital. This was a patient with advanced stage of breast cancer who was unable to get transport to a tertiary level facility. The mortality index for the two tertiary hospitals was 18.6% (SBAH) and 10.15% (KAH) and 12.5% for the level 2 hospital.

1.3.6 Table 5 Markers for classification of a maternal near-miss.

Near-miss marker	Number (%)
Cerebrovascular accident	2 (1.70)
Total paralysis	1 (0.85)
Oxygen saturation <90% for > 60 minutes	6 (5.13)
Acute thrombocytopenia (<50 000 platelets)	26 (2.22)
Creatinine > 300umol/l or > 3.5mg/dl	4 (3.42)
Bilirubin > 100umol/l or > 6.0 mg/dl	1 (0.85)
Ketoacids in urine	4 (3.42)
Use of continuous vasoactive drug	3 (2.56)
Dialysis for acute renal failure	2 (1.70)
Hysterectomy following infection or haemorrhage	35 (29.91) (infection=14, haemorrhage = 21)
Cardio-pulmonary resuscitation	3 (2.56)
Transfusion of > 5units red cell transfusion	31 (26.50)
Intubation and ventilation for > 60 minutes	18 (15.38)

1.3.7 Table 6 Organ system dysfunction in women with life-threatening conditions (*N*=136)*

	number	percentage
Vascular dysfunction (hypovolemia)	54	40.0%
Uterine dysfunction	35	25.74%
Coagulation dysfunction	27	19.85%
Respiratory dysfunction	24	17.65%
Cardiovascular dysfunction	9	6.61%
Immunological dysfunction	8	5.89%
Renal dysfunction	8	5.89%
Cerebral dysfunction	7	5.15%
Hepatic dysfunction	5	3.68%
Metabolic dysfunction	5	3.68%

*Some women had more than one organ dysfunction

1.3.8 Table 7 Comparison of the indices of severe acute morbidity rates at the Pretoria Academic Complex for the periods 1997-1998, 2002-2004 and 2013-2014.

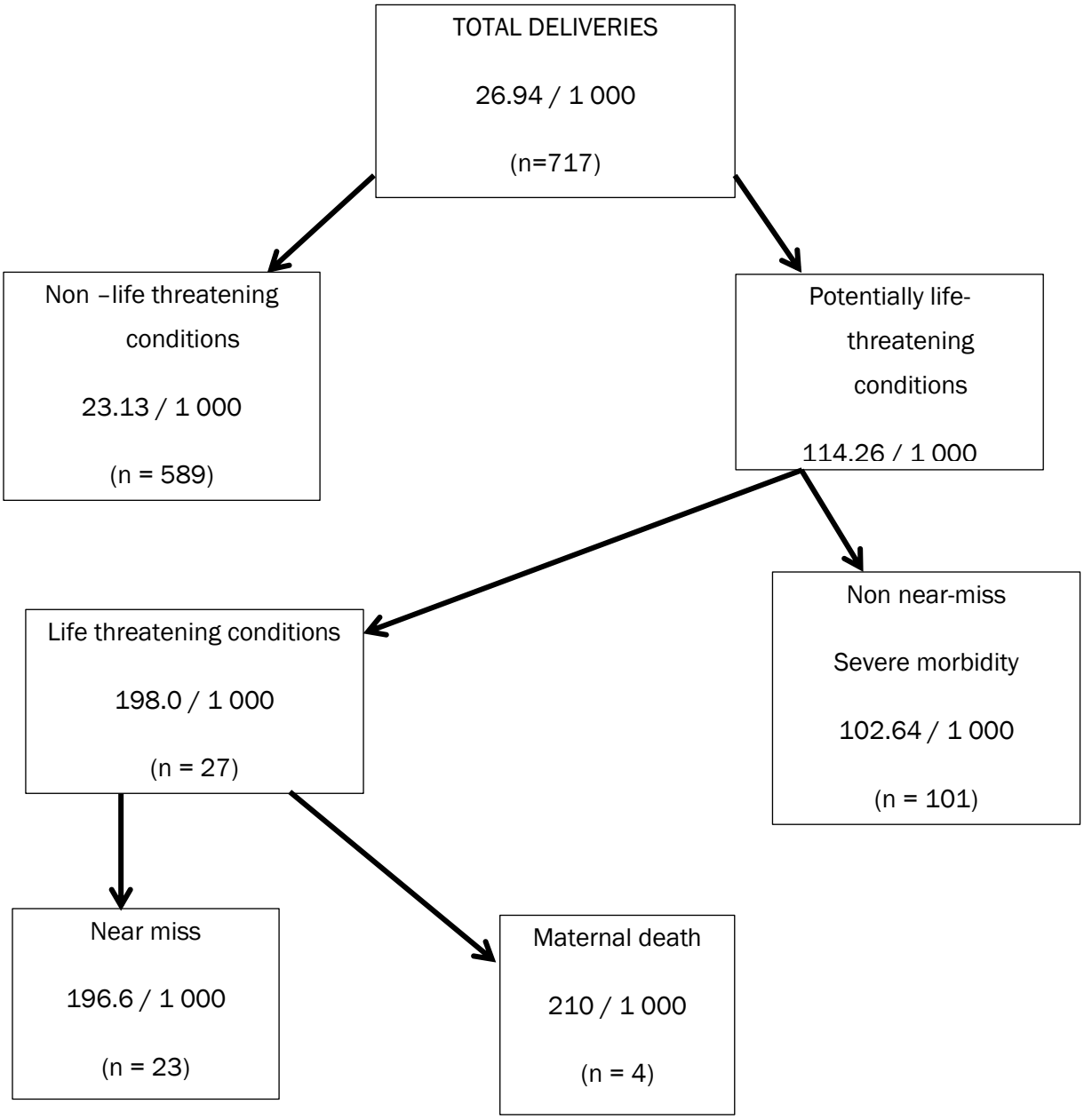
	1997-1998			2002-2004			2013-2014		
	SMOR	iMMR	MI	SMOR	iMMR	MI	SMOR	iMMR	MI
Antepartum haemorrhage	1.04	0	0	0.91	1.9	2.1	0.6	0	0
Postpartum haemorrhage	1.41	7.4	5.3	2.06	15.5	7.5	1.2	3.8	3.2
Hypertension	1.48	33.3	22.5	1.57	19.42	12.3	1.6	22.5	13.6
Puerperal sepsis	0.37	7.4	20.0	0.54	5.8	10.7	0.5	0	0
Non-pregnancy related infections	0.33	22.2	66.7	0.41	19.4	47.6	0.8	22.5	30.0
Medical and surgical disorders	0.78	11.1	14.3	0.82	11.7	14.3	0.8	15.0	19.0
Total (excluding early pregnancy losses)	5.8	96.2	16.6	7.0	85.5	12.2	5.1	71.4	14.0

Although the SMOR for the general population has remained the same since 1997-1998, both the iMMR and the MI have decreased. These findings are consistent for postpartum haemorrhage and hypertension. The SMOR for puerperal sepsis has remained constant despite the HIV epidemic with a decrease in mortality index. The SMOR and mortality index for medical and surgical conditions remain unchanged.

Figure 3 illustrates the perinatal mortality related to maternal morbidity. The women with severe maternal morbidity and mortality had a much higher perinatal mortality rate (PNMR), however for every woman with a complicated pregnancy

almost 5 women had no life threatening condition. This explains the relatively small difference between the total PNMR and the PNMR of the non-life threatening conditions.

1.3.9 Figure 3 Perinatal mortality rate (for babies > 500g)



The primary obstetric causes of perinatal death were unexplained intra-uterine death (30.3%), spontaneous preterm labour (25.5%), ante-partum haemorrhage (12.3%), intra-partum asphyxia (9.3%), hypertensive disorders (7.4%), fetal abnormality (6.9%) and maternal disease (3.7%).

1.4 DISCUSSION

To our knowledge this is the first study in South Africa assessing the spectrum of morbidity for a specific region. There were 26 614 deliveries over a 12-month period (2013-2014). This is almost a doubling of deliveries since 1997-1998 when the total number of births for the biennium was 27 025 and a 35% increase since 2002-2004 (51 469 births for the triennium 2002-2004).[6] Just over 4% of women developed a potentially life-threatening condition and 0.5% developed a life-threatening condition. This is lower than the WHO Multicountry Survey on maternal and newborn health which reported an incidence of 7% for potentially life-threatening conditions and 1% for life-threatening conditions.[4] However the difference between the 2 studies was that our was population-based while the WHO study was hospital-based.

About 40% of women with acute life-threatening conditions did not present directly to the two tertiary level hospitals during the acute stage of disease. These patients were booked at a level 1 or 2 facility and then developed an acute condition requiring urgent transfer. Severe preeclampsia, obstetric haemorrhage and organ dysfunction due to an underlying medical condition were the most important reasons for emergency transfer. This indicates the necessity of having all health care professionals involved in care of pregnant women trained in the initial stabilisation and management of obstetric and neonatal emergencies. The antenatal care protocol used in our complex is based on the WHO recommendation of four antenatal visits for low risk patients.[7] The low frequency of visits possibly means that cases of preeclampsia in the early stages of the disease process were missed leading to

patients presenting at a later stage with acute complications requiring tertiary care. This might mean revision of our current antenatal care protocol is required. This is supported by the recent Cochrane review on patterns of routine antenatal care for low-risk pregnancy.[8]

There has been a decrease in the iMMR and MI at the PAC since 1997. This has been associated with decreases in MI for postpartum haemorrhage, hypertension, puerperal sepsis and non-pregnancy related infections. The mortality index for non-pregnancy related infections in the Pretoria Academic Complex was 66.7% in 1997-1999, 75% in 2000, 47.6% from 2002-2004 and 30% during this study period.[6,9] The decrease reflects the implementation of the anti-retroviral program by the Department of Health and better handling of respiratory complications. Of significance is the low mortality index for postpartum haemorrhage (3.2%) which is less than half of the rate (7.5%) reported in 2002-2004 and significantly lower than of the rate (5.3%) reported in for the period 1997-1998.[9.10] The decrease in MI for severe postpartum haemorrhage and puerperal sepsis is most likely as a result of the introduction of strict protocols while the reduction in MI for hypertension may be due to the implementation of calcium supplementation for patients at risk. The frequency of postpartum haemorrhage in women with life threatening conditions (22.7%) was similar to that of the WHO study (26.7%).[4] However the rates of preeclampsia (29.41%) and non-pregnancy related infections (14.7%) was greater in our study (WHO 16.3% and 1.6% respectively). The rate of preeclampsia in women with life-threatening conditions was consistent with reports from Nigeria (32.5%) and Mozambique (32.9%).[11,12]

Vascular (hypovolemia), uterine (hysterectomy) and coagulation (low platelets) dysfunction were the most frequent organ system dysfunctions in women with life-threatening conditions (table 6). Many women had multiple complications. The disease profile in our complex has changed since the year 2000 when vascular, cardiac, immunological and coagulation dysfunction were the most

important organ systems causing obstetric morbidity.[13] Obstetric haemorrhage was the potentially life-threatening condition most frequently encountered in our complex (37.5%) and vascular dysfunction as a result of hypovolemia was the most common organ system dysfunction seen. The low mortality index for postpartum haemorrhage suggests that although postpartum haemorrhage is an important problem, the condition is well managed by our clinicians.

Of the five potentially life-threatening conditions, hypertensive disorders contributed to 7.4% of perinatal deaths. Ninety-two point six percent of perinatal deaths were not related to antepartum and intrapartum maternal life-threatening conditions, and if postpartum maternal life-threatening conditions are included then 80% of perinatal deaths did not have severe morbidity. These findings are consistent with that Allanson et al describing perinatal mortality in the Mpumalanga Province and Vogel et al in the WHO Mutlti-Country Survey who found that a significant proportion of women have no recognisable obstetric or medical condition at the time of perinatal death.[14,15] The WHO Multi-Country Survey found a maternal complication rate of 22.9%, 27.7% and 21.2% in late macerated stillbirths, late fresh stillbirths and early neonatal deaths respectively and Allanson et al found a rate of maternal complications in macerated stillbirths, fresh stillbirths and early neonatal deaths of 50.4%, 50.7% and 25.8% respectively. Current early antenatal identification of both severe maternal morbidity and perinatal mortality is inadequate.

The strength of this paper is the robust method of data collection. The new national birth register records maternal complications facilitating the collection of data. The Pretoria Academic Complex has been collecting and reviewing data on life-threatening conditions for more than 15 years and all the doctors are familiar with the WHO near miss criteria. Women who were classified as a near miss were interviewed about barriers encountered in accessing healthcare. This information will be presented in a separate paper.

The limitations of this study are the exclusion of cases of early pregnancy loss (abortions and ectopic pregnancies) and some cases of sepsis may have been missed if patients presented late in the postpartum period. Further, maternal infections like pneumonia, tuberculosis, meningitis were not on the list of potentially life-threatening conditions, and thus the SMOR could not be calculated for this. The list of potentially life-threatening should be expanded to include medical conditions and non-pregnancy related infections. This is supported by Lumbiganon et al who demonstrated that indirect causes of maternal deaths are increasingly important in developing countries with indirect causes being responsible for about one-fifth of severe maternal outcomes.[16]

1.5 RECOMMENDATIONS

- The World Health Organisation has identified 5 potentially life threatening conditions: severe postpartum haemorrhage, severe preeclampsia, eclampsia, sepsis/severe infection and ruptured uterus.[2] Our study has shown that conditions such as abruptio placenta, non-pregnancy related infections and medical and surgical disorders are also important causes of obstetric morbidity and the WHO should therefore consider expanding their categories of potentially life-threatening conditions.

- Forty-percent of patients with life-threatening conditions presented to a level 1 or 2 facility before being transferred for tertiary care. Cases of postpartum haemorrhage and severe pre-eclampsia could not be predicted antenatally. In addition, no recognisable obstetric condition was present in majority pregnancies that ended in a perinatal death. Health workers in level 1 and 2 centres must therefore be able to recognise, stabilise and transfer pregnant women and neonates presenting with an acute obstetric emergency.

- Strategies to prevent and screen for preeclampsia and improvement of emergency transport for women are essential in order to reduce obstetric morbidity and mortality.
- Review of the reduced visits protocol put forward by the WHO should be considered as increasing the frequency of ante-natal visits for low risk women may increase detection of pre-eclampsia at an earlier stage of the disease process.[7] However, this would require considerable increase in resources.

1.6 CONCLUSION

This study was able to identify the proportion of pregnancy-related morbidity in our population and compare it to other studies. The mortality index and prevalence of potentially life-threatening conditions were similar to the WHO Multicountry Survey. Although there has been a decrease in the mortality index for non-pregnancy related infection, further interventions need to be implemented to reduce morbidity and mortality associated with HIV-disease and tuberculosis. A significant proportion of women who developed severe maternal conditions were not identified during the ante-natal period indicating the necessity of ensuring all levels of care can manage the initial steps in obstetric and neonatal emergencies and an efficient emergency transport system is available.

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CHAPTER 2

Barriers to obstetric care amongst maternal near-misses

Aims and objectives

The objective of the study was to determine the delays/barriers in providing obstetric care to women who classified as a maternal near-miss.

Methods

This was a descriptive observational study at Steve Biko Academic Hospital, a tertiary referral hospital in Pretoria, South Africa. One hundred cases of maternal near-misses were prospectively identified using the WHO criteria. The "three delays model" was used to identify the phases of delay in the health system and recorded by the medical physician caring for the patient.

Results

One or more factors causing a delay in accessing care were identified in 83% of near-miss cases. Phase I and III delays were the most important causes of barriers. Lack of knowledge of the problem (40%) and inadequate antenatal care (37%) were important first phase delays. Delay in patient admission, referral and treatment (37%) and sub-standard care (36%) were problems encountered within the health system. The above causes were also the most important factors causing delays for the leading causes of maternal near-misses - obstetric haemorrhage, hypertension/preeclampsia and medical and surgical conditions.

Conclusion

Maternal morbidity and mortality rates may be reduced by educating the community about symptoms and complications related to pregnancy. Training healthcare workers to identify and manage obstetric emergencies is also important. The frequency of antenatal visits should be revised with additional visits in the third trimester allowing more opportunities for blood pressure to be checked and for identifying hypertension.

2.1 INTRODUCTION

Obstetric emergencies may occur in women with known risk factors (pre-existing medical disease or recurrent miscarriage) or may be caused by pregnancy itself, gestational hypertension or obstetric haemorrhage. A significant proportion of serious complications occur in pregnancy in women with no recognisable risk factors.[1,2] A serious complication may progress rapidly to a life-threatening situation. Access and timely referral to appropriate emergency obstetric care are therefore important components of the health-care system. The World Health Organisation (WHO) estimates that about 88-98% of maternal deaths can be avoided with timely access to existing emergency obstetric intervention.[3] However there is growing evidence that the majority of near-miss cases in developing countries arrive at referring hospitals in a critical condition.[4]

Several factors may influence a woman's ability to access appropriate obstetric care. Thaddeus and Maine developed the three delays model in 1994.[5] The model evaluates circumstances surrounding access to appropriate emergency obstetric care. The 3 components are: Phase I Delay - *delay in deciding to seek care by the individual and/or family,* Phase II Delay - *delay in reaching an adequate health care facility* and Phase III Delay - *delay in receiving adequate care at the health facility.* Several authors have used the "three delays model" to investigate delays related to maternal morbidity and mortality.

A maternal near-miss is defined as a woman who nearly died but survived a complication that occurred during pregnancy or childbirth.[6] Studying circumstances around near-miss cases have an advantage over maternal death cases because near-miss patients are able to provide direct information after an event.

2.2 OBJECTIVES

To determine the reasons for delay in accessing appropriate obstetric care for women who are classified as maternal near-misses.

2.3 METHODS

This was a descriptive observational study performed at Steve Biko Academic Hospital (SBAH) from 1 August 2013 to 30 October 2015. Steve Biko Academic Hospital is a tertiary referral hospital which serves as a referral hospital for the central and eastern Tshwane regions. Patient referrals are mainly from a level 1 hospital (Tshwane District Hospital) which is situated adjacent to Steve Biko Academic Hospital and a level 2 Hospital (Mamelodi Hospital), in Tshwane east. Very ill patients may be referred directly from mid-wife obstetric units in the referral area. Obstetric patients with underlying medical disease may be referred in from neighbouring provinces.

One hundred near-miss cases were prospectively identified at daily audit meetings at SBAH using the WHO criteria for a maternal near-miss.[7] Data was recorded by the physician caring for the patient. Information on antenatal care was obtained from case-notes recorded on the patient's antenatal card, maternity case record and from patient interviews. The antenatal care schedule for low risk patients, adopted by our district is based on the WHO model of reduced visits: booking, 20, 26, 32, 38 weeks with an appointment at the hospital at 41 weeks. The three delays model described by Thaddeus and Maine[5] was used to evaluate reasons for delay. Table 1 describes the factors within each phase that were evaluated in the study. Phase III delays include all delays within the health-system: from the moment a patient presents to a health facility, irrespective of the level of care, until she receives the appropriate care for her condition.

2.3.1 Table 1. The three delays model

A. Community level factors associated with delay in seeking healthcare (Phase I)
Desire for home-delivery
Lack of knowledge of the problem
Inadequate antenatal care (late attendance/delayed visits)
Non-compliance with health providers advice
Belief in alternative care
Family member prevented you from accessing healthcare
B. Factors associated with delay in reaching the health system (Phase II)
Lack of finance
Lack of transport
C. Factors associated with delays within the health system (Phase III)
Delay in patient admission, referral or treatment
Lack of resources (blood/ICU)
Sub-standard care (inappropriate diagnosis or treatment)

Descriptive statistics in the form of means and standard deviations in the case of continuous data and frequencies and percentages in the case of categorical data were calculated. Ethical approval was obtained from the University of Pretoria Ethics Committee (No 125/2013).

2.4 RESULTS

Data were collected for 100 maternal near-miss cases. Forty-one patients were referred in from other institutions while 59 patients were known to our hospital or presented directly with an acute obstetric emergency. Information on antenatal history and monitoring is shown in table 2.

2.4.1 Table 2 Ante-natal history and monitoring

Age	years
Mean (SD)	29.7 (+/- 6.3)
Range	17-46
Parity	
Mean (range)	1.4 (0-4)
Medical history	number
Chronic hypertension	6
Diabetes mellitus	7
Cardiac disease	10
Other	12
Timing of event	
Antenatal	62
Intra-partum	7
Postpartum	31
Presence of obstetric complications during pregnancy	
Yes	23
No	67
Unknown/unbooked	10

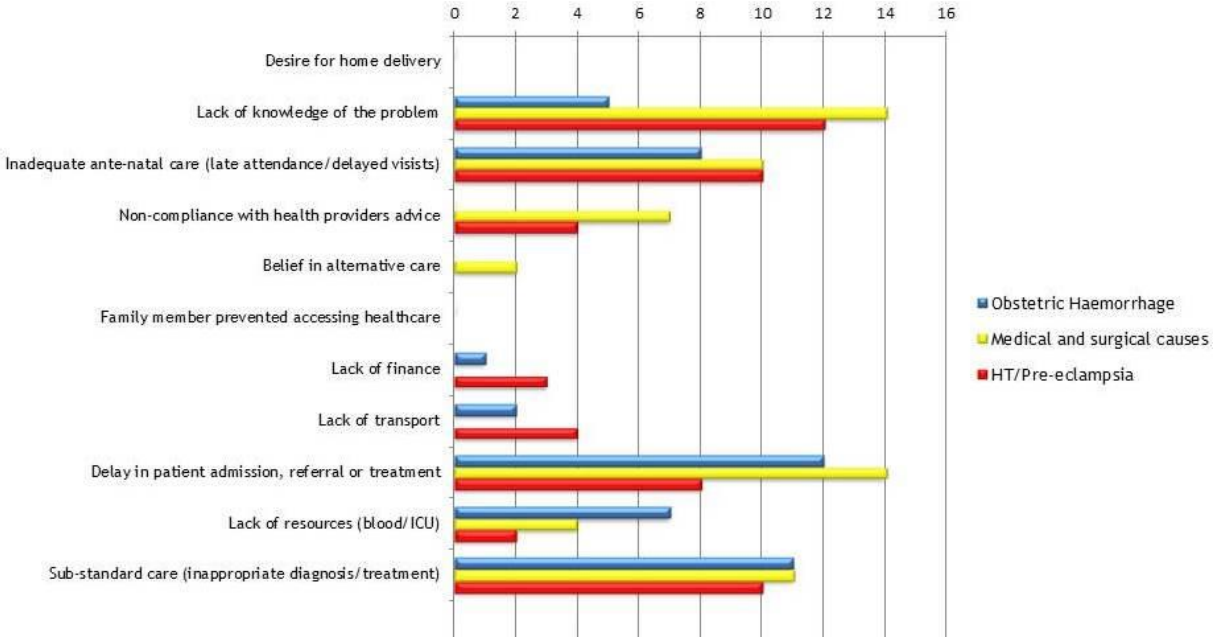
The most important obstetric causes for a maternal near-miss were obstetric haemorrhage (n=31), medical and surgical disorders (n=31) and complications of hypertension and pre-eclampsia in pregnancy (n=24). One or more factors causing a delay in accessing care were identified in 83% of near-miss cases (Table 3).

2.4.2 Table 3 Barriers to accessing care for maternal near-misses

Community level factors associated with delay in seeking healthcare(Phase I)	**Numbers**
Desire for home-delivery	0
Lack of knowledge of the problem	40
Inadequate antenatal care (late attendance/delayed visits)	37
Non-compliance with health providers advice	16
Belief in alternative care	6
Family member prevented you from accessing healthcare	2
Factors associated with delay in reaching the health system (Phase II)	
Lack of finance	6
Lack of transport	8
Factors associated with delays within the health system (Phase III)	
Delay in patient admission, referral or treatment	37
Lack of resources (blood/ICU)	14
Sub-standard care (inappropriate diagnosis or treatment)	36

Phase I and III delays, in particular, lack of knowledge of the problem (40%), inadequate antenatal care (37%), delay in patient admission, referral and treatment (37%) and sub-standard care (36%) were the most common factors in the study population. These factors were also the most important contributors when separately analysing cases of obstetrics haemorrhage, medical and surgical disease and hypertension in pregnancy. (Figure 1)

2.4.3 Figure 1 Barriers to accessing care for cases of obstetric haemorrhage, medical and surgical disorders and hypertension and pre-eclampsia



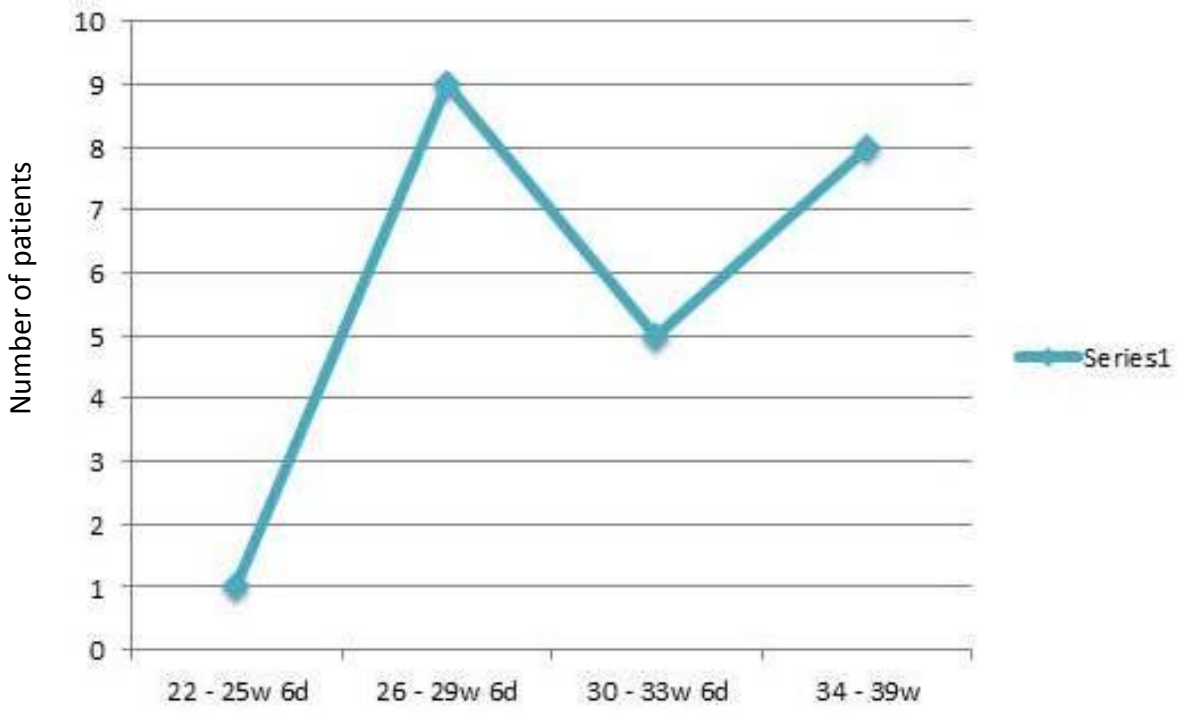
Number of patients

The near-miss events amongst hypertensive patients occurred between 24 and 38 weeks gestation with most events occurring between 26 and 38 weeks (Table 4 and figure 2). Five (21%) of hypertensive near-misses were unbooked while booking information was not available for 4 (17%) patients. The average time between the last antenatal visit and the near-miss event was 2.6 weeks.

2.4.4 Table 4 Timing of events of hypertensive near-misses

Patient number	Gestational age of near-miss event	Gestational age of last antenatal clinic visit prior to near-miss event
1	31	29
2	32	28
3	24	unbooked
4	26	26
5	36	36
6	37	32
7	30	26
8	35	unbooked
9	38	37
10	28	28
11	32	26
12	29	29
13	37	unknown
14	39	unbooked
15	postpartum	Normotensive at delivery
16	34	32
17	27	24
18	27	unbooked
19	30	26
20	26	unbooked
21	37	unknown
22	37	32
23	30	unknown
24	33	unknown

2.4.5 Figure 2 Gestational age at which hypertensive near-miss events occurred



Phase III delays were significant barriers encountered by patients with obstetric haemorrhage. Delay in recognising the problem of bleeding, delay in initiating steps to stop bleeding and delay in patient transfer were the problems identified in 75% of cases. Lack of intensive care beds and lack of blood and blood products were problems observed in 16.8% of cases. There were 2 cases of ante-partum haemorrhage in patients with undiagnosed placenta praevia. Both patients were booked but placental location was not recorded on the ultrasound report. There were 3 cases of uterine rupture. Two patients had unsafe terminations of pregnancy requiring hysterectomy; the other patient had 2 previous caesarean sections, was unbooked and presented in labour with a uterine rupture. Obstetric haemorrhage related to abruptio placenta was an important cause of morbidity. Inadequate antenatal care for abruptio related to hypertension and delay in patient transfer were important avoidable factors.

There were 6 cases of maternal near-misses due to parasuicide/unsafe termination of pregnancy. In these cases lack of knowledge of the problem

(4/6), inadequate antenatal care (5/6) and non-compliance with health-worker advice were the most important barriers identified. These were also the most important factors in cases of non-pregnancy related infections.

2.5 DISCUSSION

This study shows an unacceptably high rate of barriers encountered by obstetric patients during pregnancy. Sixty-six percent of near-miss patients encountered more than 1 delay. Inadequate antenatal care and lack of the patient's knowledge of the underlying problem were important Phase I delays. Inadequate antenatal care was a problem in 37% of cases. This is similar to the rate of 30% found in a Brazilian study.[8] The authors also found an association between delay in seeking health services and maternal near-miss and maternal death. Delay in seeking health services was 2.5 times more frequent in maternal near-miss patients and increased 6-fold in mothers who died. More than a quarter of our patients (29% of pre-eclamptic near-misses and 26% of near-misses with medical disease) had risk factors for hypertension in pregnancy or had an underlying medical condition but booked after 20 weeks gestation or had inadequate antenatal care due to non-compliance with the required antenatal visits. Several studies in lower-and-middle income countries have shown that women are unable to judge the severity of their disease pathology and may only seek care once their condition becomes life-threatening.[9,10,11] This highlights the need for community education about pregnancy risks. This may be achieved by encouraging all women to register with cell-phone/web-based sites like MomConnect. After a complicated pregnancy, mothers should also be counselled about future pregnancy risks.

All of the hypertensive near-miss events occurred between 24 and 39 weeks with peaks between 26 and 39 weeks. Almost sixty percent of these patients booked for antenatal care but their acute condition could not have been detected in time with the current protocol of antenatal visits. Similarly, the

England Collaborative Group reported that a significant proportion of serious complications occur in women with no recognisable risk factors.[2] The antenatal care protocol used in our complex is based on the WHO recommendation of four antenatal visits for low risk patients.[12] Unfortunately this protocol was unable to timeously detect and prevent an acute hypertensive emergency. The average time between the last antenatal visit and the near-miss event was 2.6 weeks. The period between antenatal visits using our current guidelines is 6 weeks. This time-period is too infrequent to detect significant changes in blood pressure. The current guideline on the frequency of antenatal visits should be revised as additional visits, especially in the 3rd trimester, should be implemented. Blood pressure must be recorded at every visit. Alternatively, an integrated approach to antenatal care could be considered whereby a pregnant mother visits a day-clinic, undertakes home-monitoring or is examined by an occupational nurse at the work-place where she is able to record her blood pressure every 2 weeks from 24 weeks gestation.

Delay in patient admission, referral and treatment and sub-standard care were important barriers identified for near-miss cases related to haemorrhage, hypertension and medical disease in pregnancy. Obstetric haemorrhage is a medical emergency that requires timely diagnosis and aggressive resuscitation and management by the labour-ward team. Fire-drills in obstetric emergencies should be practised by labour-ward teams. The National Committee for the Confidential Enquiry into Maternal Deaths in South Africa has proposed a referral algorithm for patients with underlying cardiac and medical disease in pregnancy.[13] All patients with underlying medical disease should be risk assessed and referred timeously to the appropriate level of care. Such protocols should also be followed for other obstetric emergencies.

2.6 STRENGTHS AND LIMITATIONS

This is the first study in South Africa where near-miss patients provided a direct account of obstacles they had to overcome before receiving the appropriate form of healthcare.

This study is limited as it involves only one tertiary institution, but we believe a similar picture would occur at other sites as the delays detected are commonly found in maternal deaths due to hypertension.[13]

It is unknown how many cases with hypertension were detected and managed appropriately. However, given the high institutional Maternal Mortality Ratio (iMMR) of hypertension in pregnancy, and that the iMMR has been relatively constant for a decade suggests a health system problem in detecting and managing hypertension. The problem (of a protocol of reduced antenatal visits) has been clearly demonstrated in this study.

2.7 CONCLUSION

Obstetric morbidity may be reduced by overcoming barriers preventing patients from accessing care. Healthcare managers need to continually assess and revise policies to improve obstetric care. This study has shown that the current schedule of antenatal care visits should be revised so that women are seen more frequently during pregnancy where blood pressure can be monitored. Patient education and health- care worker training needs to be strengthened.

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CHAPTER 3

Cerebral white matter lesions after pre-eclampsia

Background
Women who have had pre-eclampsia in their previous pregnancies demonstrate a greater prevalence of cerebral white matter lesions several years after the pregnancy than women who have been normotensive during their pregnancy. Both the pathophysiology and the timing of development of these lesions are uncertain. White matter lesions, in the general population, are associated with an increased risk of stroke, dementia and death.

Aims and objectives
The objective of the study was to determine the prevalence of cerebral white matter lesions amongst women with severe pre-eclampsia at delivery, 6 months and 1 year postpartum and to establish the possible pathophysiology and risks factors.

Methods
This was a longitudinal study performed at Steve Biko Academic Hospital, a tertiary referral hospital in Pretoria South Africa. Ninety-four women with severe pre-eclampsia were identified and recruited during the delivery admission. Magnetic resonance imaging (MRI) of the brain was performed post – delivery and at 6 months and 1 year postpartum.

Results
Cerebral white matter lesions were demonstrated in 61.7% of women at delivery, 56.4% at 6 months and 47.9% at 1 year. Majority of the lesions were found in the frontal lobes of the brain. The presence of lesions at 1 year post-delivery was associated with the number of drugs needed to control blood pressure during pregnancy (OR 5.1, 95% CI 2.3-11.3, $p < 0.001$). The prevalence of WMLs at 1 year was double in women with chronic hypertension at 1 year compared to those women who were normotensive (65.1% vs 32.3%).

Conclusion

Women who require 2 or more drugs to control blood pressure during pregnancy have an increased risk of developing cerebral white matter lesions after delivery.

3.1 INTRODUCTION

Pre-eclampsia is a pregnancy specific disorder characterised by new onset hypertension after 20 weeks gestation. The pathogenesis of pre-eclampsia is still poorly understood but it is widely established that the disease contributes to gross maternal vascular dysfunction.[1] Cerebrovascular abnormalities are an important complication and neurological symptoms are often reported. Cerebral complications are the single most common cause of hypertensive maternal deaths in South Africa.[2]

Pregnancy is associated with significant changes in both the cardiovascular and cerebral circulations.[3] Physiological changes such as decreased vascular resistance, hyperpermeability and increased cardiac output are necessary to perfuse vital organs such as the placenta and uterus.[3] Hemodynamic changes in the brain such as increased permeability of cerebral vessels increase the potential for development of oedema, raised intracranial pressure and other neurological symptoms.[4] Additionally, a rapid rise in blood pressure during the pre-eclamptic process can result in disruption of the cerebral autoregulation mechanism and blood-brain barrier.[5]

The posterior reverse encephalopathy syndrome (PRES) is a condition characterised clinically by headaches, altered mental status, seizures, blurred vision and distinct MR imaging appearance.[6] It is currently believed that the pathophysiological process of PRES is responsible for the cerebral oedema in pre-eclamptic women who present with neurological symptoms.[6] Magnetic resonance imaging usually reveals widespread hemispheric watershed vasogenic oedema concentrated mainly in the parietal and occipital lobes of the brain.[7] Both clinical symptoms and radiological findings resolve after eliminaton of etiological factors.[8] Brain lesions associated with PRES are thought to be the result of the disturbance of the cerebral autoregulation mechanism and impairment of endothelial function.[9] Cerebral autoregulation is the ability of

the cerebral vasculature to maintain a stable cerebral blood flow within a certain range of blood pressure values.[10] This is facilitated by constriction in conditions of high blood pressure and dilatation when blood pressure is low.[11] Cerebral blood flow remains stable if the mean arterial blood pressure does not exceed 150mmHg or falls below 50-60mmHg.[11] Disruption of the autoregulation mechanism occurs with forced vasodilatation of the cerebral resistance vessels and subsequent hyperperfusion when blood pressure exceeds the upper limit of autoregulation. The cerebral autoregulation mechanism consists of myogenic and neurogenic components.[9] Endothelial damage deceases the functional effect of the myogenic mechanism.[12] In these conditions regulation of cerebral perfusion is taken over by neurogenic mechanisms. Areas of the brain that are poorly innervated by sympathetic nerves (posterior circulation areas) become sensitive to blood pressure elevation and extravasation of fluid occurs when elevation in blood pressure exceeds the autoregulation capacity of blood vessels in the brain.[7] Lesions associated with PRES are therefore often demonstrated in the posterior aspects of the brain. Anterior parts of the brain which have a greater sympathetic supply are protected from overperfusion by a vasoconstrictive effect.[7] Early diagnosis and treatment of clinical features associated with PRES may result in total resolution of both radiological and clinical features.[13]

White matter lesions or "leukoaraiosis" refers to neuroimaging abnormalities of the cerebral white matter which are visible as bilateral and either patchy or diffuse areas of hypodensity on CT or hyperintensity on T2-weighted MRI.[14] Although the pathogenesis of cerebral white matter lesions is unknown, cerebral ischemia is believed to play an important role.[14] These lesions are frequently observed on neuroimaging modalities in the ageing population and persons who have a history of stroke.[14] Other risk factors include arterial hypertension, diabetes mellitus and cardiac disease.[14] In the general population, the prevalence of cerebral white matter lesions varies between 11-21% in adults aged 64 to 94% at the age of 82.[15] How hypertension or ageing contribute to white matter lesions is uncertain but WMLs in both the elderly

and hypertensive patients are possibly the result of damage to cerebral small vessels.[16] Raised blood pressure, and other vascular disorders cause alterations of the small arteries and arterioles of the cerebral white matter. Smooth muscle cells are replaced by fibo-hyaline material causing thickening of vascular walls and narrowing of their lumen.[14] It is believed that these alterations in cerebral vasculature cause a reduction in blood supply to white matter and this further leads to localised ischemic areas of necrosis or diffuse leukoaraiosis which is irreversible. Furthermore WML progression has been found to be less in controlled treated hypertensives compared with uncontrolled untreated hypertensives.[17,18] White matter lesions due to cerebral small vessel disease are not related to WMLs due to PRES as the distribution of lesions is different and WMLs due to PRES are reversible.

Recently studies have demonstrated an increased prevalence of cerebral white matter lesions in formerly pre-eclamptic women.[19,20] Aukes et al have reported a prevalence, at 5-6 years after delivery, of 41% in formerly eclamptic, 37% in formerly pre-eclamptic women compared with 17-21% in a control group of normotensive patients.[19,20] The aim of this study was to assess the presence and severity cerebral white matter lesions amongst pre-eclamptic patients at delivery, 6 months and 1 year postpartum and determine the possible pathophysiology and associated risk factors.

3.2 METHODS

This was a longitudinal study of maternal near misses and women with potentially life-threatening complications at Steve Biko Academic Hospital from 1 April 2013 to 30 March 2016. Recruitment of pre-eclamptic patients for this phase of the study took place from 1 April 2013 – 30 March 2015 and follow-up visits took place from 1 April 2014 – 30 March 2016. The Radiology Department at Steve Biko Academic Hospital reserved MRI-imaging appointments every Monday during the study period. Post-partum women (day 2-7) with severe pre-

eclampsia were identified on a Monday morning and if fit to be transported to the MRI unit were informed of the study. MRI studies were performed on patients who consented to the procedure and were agreeable to follow-up studies. Follow-up scans were performed at 6 months and 1 year postpartum. When studying follow-up MRI scans, the radiologist was able to compare studies at delivery to determine whether lesions had enlarged or regressed. The radiologist also looked for new emerging lesions.

As per hospital protocol, all patients with severe pre-eclampsia were managed expectantly until 34 weeks if maternal and fetal condition was satisfactory. Magnesium sulphate was administered to pre-eclamptic women for the following indications:

- Treatment of eclamptic convulsions
- Symptoms and signs of imminent eclampsia such as severe headaches, visual disturbances and/or epigastric pain
- Prior to transport of patients with severe acute hypertension from referring centres.

The first-line therapy for the treatment of hypertensive disorders in pregnancy was oral methyl-dopa. The second and third line agents to control blood pressure were an oral calcium channel blocker (nifedipine or amlodipine) and prasozin. Nifedipine short-acting (10mg) or intravenous labetalol was used for the management of severe acute hypertension in pregnancy. The goal of treatment was to maintain a systolic blood pressure of 140-160 mmHg and a diastolic blood pressure of 90-110 mmHg. Hypertensive disorders were classified according to the classification and diagnosis of the International Society for the Study of Hypertension in Pregancy (ISSHP).[21] The following definitions were used:

Severe hypertension/uncontrolled – blood pressure > 160/110 mmHg

Low blood pressure – blood pressure < 100/60 mmHg

Rescue therapy – short acting anti-hypertensive treatment administered if blood pressure is > 160/110 mmHg

Episodes of severe hypertensive days – number of days during which a blood pressure of 160/110 mmHg or more was recorded

The MRI studies were performed on a 1.5 Tesla Phillips Achieva System at the Radiology Department at Steve Biko Academic Hospital, Pretoria, South Africa. Five millimetre slices with a 20% gap and a matrix of 256x256 was used. The sequences used were: T1 sagittal (repetition time (TR) = 2.11ms; echo time (TE) = 2.4ms), FLAIR axial (TR = 11 000ms; TE = 100ms), T2 axial (TR = 6059ms; TE = 100ms), T2 coronal (TR = 3281ms; TE = 100ms), Magnetic Resonance Angiography (MRA) (TR = 25ms; TE = 6.9) and Diffusion Weighted Imaging (DWI) (TR = 3518ms; TE = 89ms). The WMLs were measured according to largest diameter in categories of small (< 3mm), medium (3-10mm) or large (>10mm). The radiologist analysing the MRI images was blinded to the clinical information of the study patients.

Descriptive statistics in the form of means and standard deviations in the case of continuous data and frequencies and percentages in the case of categorical data was calculated. Binary logistic regression was used to establish if any factors had an impact on outcome. A p-value of < 0.05 was considered significant. Ethical approval was obtained from the University of Pretoria Ethics Committee (No. 125/2013).

3.3 RESULTS

There were 6536 deliveries at our hospital during the recruitment phase of the study (1 April 2013 – 30 March 2015). Four-hundred and sixty-three (7.1%) women presented with severe pre-eclampsia and of these 106 women were recruited to the study. Seven women were lost to follow-up and five declined testing at different stages of the study. Data was therefore available for 94 women. Fourteen (14.9%) women were known with chronic hypertension and developed superimposed pre-eclampsia during pregnancy. Thirty-four (36.2%) women developed HELLP syndrome and twenty-three (24.5%) were eclamptic. The demographic information for the study population is shown in Table 1

3.3.1 Table 1 Demographic data of the study population (n=94)

Race	
African, n (%)	89 (94.7%)
White, n (%)	2 (2.1%)
Coloured, (%)	2 (2.1%)
Indian, n (%)	1 (1.1%)
Age	
Mean (SD)	28.3 (6.8)
Range	18-46
Obstetric History	
Parity mean (range)	1.1 (0-4)
Medical conditions	
Chronic hypertension, n (%)	14 (14.9%)
Diabetes, n (%)	4 (4.3%)
HIV infection, n (%)	21(22.3%)
Blood pressure at presentation	
Systolic blood pressure (mmHg), mean (SD)	172.8 mmHg (30.1mmHg)
Diastolic blood pressure (mmHg), mean (SD)	108.4 mmHg (15.8mmHg)
Dipstix proteinuria on admission	

Mean (SD)	2.2+ (1.1+)
Average maternal weight at 1 year, mean (SD)	75.5kg (22.1kg)
Timing of delivery	
< 34 weeks, n (%)	47 (50.0%)
34-37 weeks, n (%)	21 (22.3%)
>37 weeks, n (%)	26 (27.7%)
Number of days from admission to delivery, mean (SD)	4.2 (7.7)
Gestational age at delivery (weeks)	
Mean (SD)	32.1 (4.3)
Minimum	25.2
Maximum	41.3
Birthweight (grams)	
Mean (SD)	1954 (835.8)
Minimum	300
Maximum	3450
Biochemical markers on admission	
Haemoglobin (g/dl) mean (SD)	12.4 (2.1)
Platelets ($x10^9$/L) mean (SD)	116.7 (90.2)
Urea (mmol/L) mean (SD)	4.4 (3.6)
Creatinine (umol/L) mean (SD)	96.2 (50.4)
Aspartate Aminotransaminase mean (SD)	139.7 (195.0)

Cerebral white matter lesions (WMLs) were found in 58 (61.7%) women at delivery, 53 (56.4%) at 6 months and in 45 (47.9%) women at 1 year. Twenty-one women showed evidence of PRES on diffusion weighted images at delivery. Of these 21 women, 9 (42.9%) demonstrated WMLs at 1 year. Therefore majority of lesions (80%) visualised at the 1 year MRI study were in women without evidence of PRES at delivery.

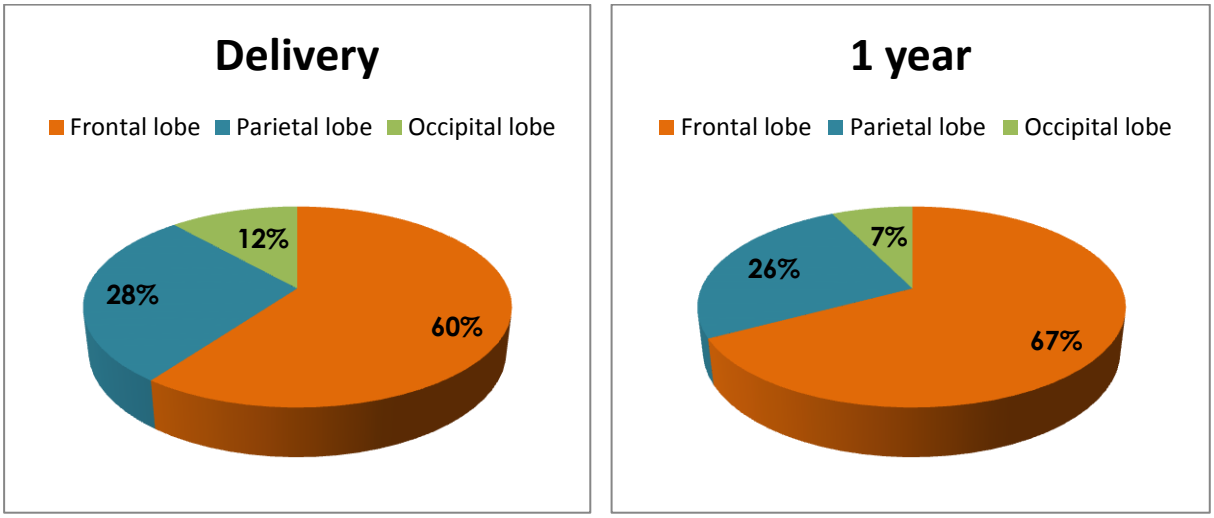
The incidence of HIV disease in the study population was 22.3%. The prevalence of WMLs was similar in the study population to that of the HIV uninfected group

suggesting that HIV disease was not responsible for the development of WMLs. Figure 1 compares the prevalence of WMLs at delivery, 6 months and 1 year between the study group and the HIV-uninfected sub-group of patients.

3.3.2 Figure 1: Prevalence of lesions in study group compared with HIV-negative group

Thirty-four (36.2%) women had no WMLs on MRI while 41 (43.6%) demonstrated lesions on all studies (delivery, 6 months and 1 year). Seventeen (18.1%) women had lesions at delivery but the WMLs were no longer present at 1 year. Twelve out of seventeen of these women, whose lesions had regressed, were normotensive at 1 year. Four women did not have lesions at delivery but WMLs were present at the 1 year scan. Of these 4 women, 3 had chronic hypertension at 1 year. Figure 2 illustrates the location of white matter lesions at delivery and 1 year. Five-percent and 2% of WMLs in the occipital and parietal lobes respectively, regressed. However there was a 7% increase in the number of lesions in the frontal lobes from delivery to 1-year postpartum.

3.3.3 Figure 2: Location of lesions at delivery and 1 year



Sixty-two percent of lesions were less than 3mm in size, 36% were 3-10mm and 2% were greater than 10mm in size. Sixty-three (67.1%) patients were diagnosed with chronic hypertension at 1 year. Sixty-five percent (n=42) of women with chronic hypertension at 1 year had WMLs compared with 32.3% (n=10) of women who were normotensive.

3.3.4 Figure 3 White matter lesions in a pre-eclamptic woman at 1 year post-delivery.

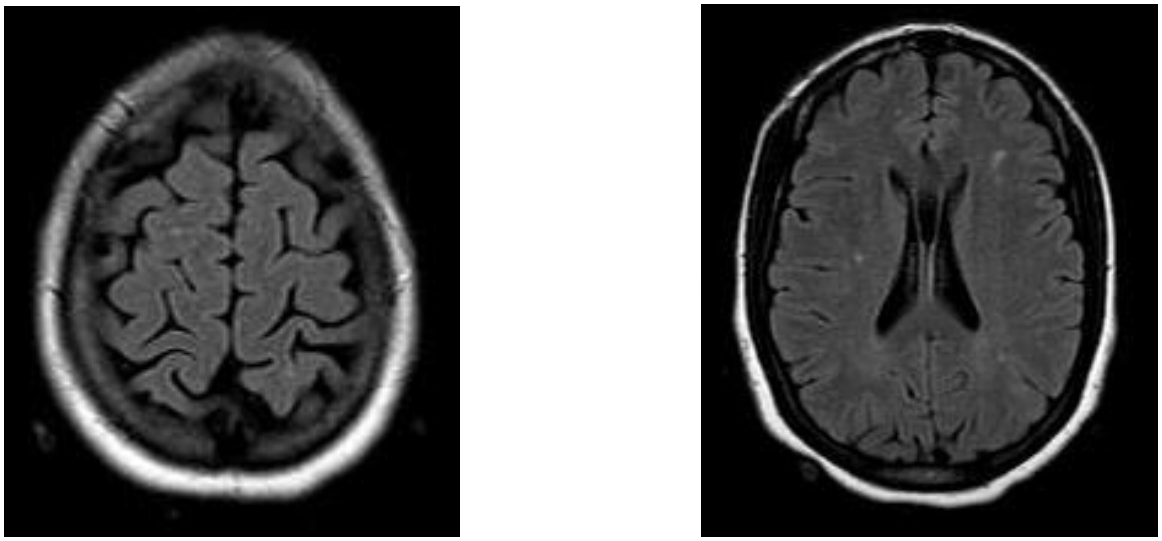


Table 2 describes the independent predictors of outcome in relation to the presence of white matter lesions at 1 year. There was no significant association between the presence of cerebral WMLs and clinical presentation of HELLP syndrome, eclampsia or early onset disease. There was also no significant difference between the clinical variables and delivery < 37 weeks.

3.3.5 Table 2 Relationship between the clinical picture at delivery and the presence of WMLs at 1 year

	1 year		*Total*	*P-value*
Potential predictors	**No WMLS n (%)**	**WMLS N (%)**		
Uncomplicated pre-eclampsia	13 (27.7%)	13 (27.7%)	26 (27.7%)	
Delivery <34 weeks	8 (17.0%)	7 (14.9%)	15 (16.0%)	
Eclampsia	3 (6.4%)	4 (8.5%)	7 (7.4%)	
Eclampsia & delivery <34 weeks	4 (8.5%)	6 (12.8%)	10 (10.6%)	P = 0.9
HELLP	6 (12.8%)	3 (6.4%)	9 (9.6%)	
HELLP & delivery <34 weeks	10 (21.3%)	11 (23.4%)	21 (22.3%)	
HELLP & eclampsia	3 (6.4%)	2 (4.3%)	5 (5.39%)	
HELLP & eclampsia & delivery <34 weeks	0 (0.0%)	1 (2.1%)	1 (1.1%)	
Total	**47 (100.0%)**	**47 (100.0%)**	**94 (100.0%)**	

Tables 3 describes the relation between blood pressure variables and the presence of white matter lesions after 1 year. The number of drugs needed to control hypertension during the ante-natal period was significantly associated with the presence of WMLs after 1 year ($p < 0.0001$).

3.3.6 Table 3 Univariate analysis of blood pressure- related variables

Blood pressure variable	Absence of WML	Presence of WML	P-Value
Mean arterial BP(mmHg)	141.9 (21.4)	140.5 (19.3)	0.75
Episodes of severe hypertensive days			
Median	1.00	1.0	0.9
Minimus	0	0	
Maximus	5.0	10.0	
Episodes of low blood pressure			
Median	0.0	0.0	0.6
Minimum	0.0	0.0	
Maximum	2.0	2.0	
Number of drugs needs to control BP			
Mean (SD)	1.28 (0.9)	2.2 (0.7)	<0.0001
Median (range)	1 (0-3)	2.0 (1-3)	
No of episodes of severe HT (> 160/110 mmHg)	2.0	2.0	
Median	0.0	0.0	0.7
Minimum	7.0	10.0	
Maximum			
No of days from admission to delivery			
Median	1.0	1.0	0.3
Minimum	0	0	
Maximum	97.0	31.0	
BMI at booking mean (SD)	30.0	31.1	0.5

3.4 DISCUSSION

Hypertension is a major contributor to a growing burden of non-communicable diseases and Africans, particularly young African women appear to be bearing the brunt of this increasing public health problem.[22] Compared to other racial groups, African women are at greater risk of developing pre-eclampsia with severe complications.[23] Almost 95% of our study population was of African origin - this may explain the slightly higher prevalence of cerebral WMLs in our study at 1 year postpartum than the rates of 41%, 37% and 34.4% found in a predominantly Caucasian population more than 5 years after the index pregnancy in the studies by Aukes and Wiegman.[19,20,24] We found that the degree of hypertension rather than clinical variation of the pre-eclamptic process such as HELLP syndrome, eclampsia and early onset disease played a role in the development of WMLs. Aukes et al also did not find any relation between the presence of HELLP syndrome, severe diastolic hypertension, neurological symptoms or the use or magnesium sulphate and the presence or severity of WMLs.[12] There was however a positive relation between early onset pre-eclampsia and current hypertension and the presence of WMLs in the study by Aukes.[20]

A systematic review of 46 studies and meta-analysis has shown that white matter lesions are an important indicator of future risk of disease, being associated with an increased risk of stroke (hazard ratio 3.3, 95% CI 2.6-4.4), dementia (1.9, 95% CI 1.3-2.8) and death (2.0, 95% CI 1.6-2.7).[15] Almost half of the pre-eclamptic women in our study were found to have cerebral WMLs 1 year after delivery. The presence of WMLs was significantly associated with the number of drugs needed to control blood pressure during the ante-natal period (OR 5.1, 95% CI 2.3-11.3, $p < 0.0001$). The average time from admission to delivery in our study was 4.2 days. The MEXPRE Latin study found a significant increase in higher maternal morbidity (37.7% versus 14.3%, $p=0.02$) in a group of pre-eclamptic women who were managed expectantly compared to prompt delivery group.[25] The authors found no neonatal benefit with a possible

increased risk of abruption and small for gestational aged infants when women with severe pre-eclampsia were managed expectantly. Bombrys et al reported a maternal complication rate of 27% among women with pre-eclampsia who were managed expectantly.[26] Complications included the development of HELLP syndrome, abruption placentae, pulmonary oedema and renal insufficiency. The authors concluded that although maternal morbidity was significant, all complications were reversible. Traditionally optimal management of severe pre-eclampsia depends on balancing the risks to the mother and fetus from pregnancy prolongation versus the risk of prematurity to the neonate from immediate delivery.[26] Expectant management of severe pre-eclampsia especially for those women requiring more than 1 drug to control hypertension is associated with increased risk of both short and long-term maternal morbidity

The pathophysiology of cerebral WMLs is presently uncertain but the distribution of the lesions may provide some insight. Currently 2 concepts regarding the pathophysiology have been proposed.[19,20,24] Aukes et al have hypothesized that WMLs may be a complication of the posterior reversible encephalopathy syndrome(PRES).[19] Oedema in PRES is typically located in the occipito-parietal lobes. White matter lesion distribution would therefore be expected primarily in the occipito-parietal areas of the brain. We found that WMLs were already present at delivery and furthermore majority of the lesions (60%) were located in the frontal lobes. This is consistent with the findings of Wiegman et al who in a follow-up of pre-eclamptic patients found that 85% of the lesions were in the frontal lobes, 35% in the parietal lobes and 11% in the temporal lobes.[24] We therefore support the suggestion by Wiegman et al that a direct causal relationship between the cerebral oedema of PRES and WMLs is unlikely. According to the vasculopathy theory, severe hypertension leads to cerebral overregulation and vasospasm.[19] Cerebral small vessel disease is the term used to describe the clinical, cognitive and neuroimaging findings resulting from an intrinsic process affecting small cerebral arterioles, capillaries and venules.[27] The key mechanism underlying brain injury secondary

to small vessel disease is ischemia which results from narrowed arteries or structural or functional occusion.[27] The vessel lumen restriction is believed to result in a state of chronic hypoperfusion of white matter, eventually resulting in degeneration of myelinated fibres.[28] This mechanism of white matter damage is the result of an incomplete infarct or selective necrosis.[29] Acute occlusion of a small vessel will lead to focal and acute ischemia and complete tissue necrosis.[28] Other mechanisms that are believed to contribute to ischemic forms of small vessel disease are blood-brain barrier damage, local subclinical inflammation and oligodendrocyte apoptosis.[28] The association between current hypertension in the study by Aukes and the number of drugs needed to achieve adequate blood pressure control in our study and the persistent presence of WMLs therefore supports the theory that hypertension per se rather than variations in clinical presention of pre-eclampsia possibly plays a role in the development of WMLs. It is also likely that these lesions developed during the ante-natal period prior to delivery.

Several studies have shown that women with pre-eclampsia have an increased risk of chronic hypertension in future life (RR 3.70; 95% CI 2.70-5.05).[30] The incidence of chronic hypertension 1 year after delivery in our study population, who had a mean age of 28 years, was 61%. This is higher than the rates reported in retrospective studies by Habli (33% over a 5 year mean follow-up period) and Sibai (6.2%).[31,32] This increased rate of chronic hypertension in our study is most likely because almost 95% of our study population was of African origin. A Nigerian study has found that not only do Africans develop more hypertension compared to other groups but hypertension is also more severe and resistant to treatment.[33] In the general population, hypertension increases the risk for the development of WMLs. A prospective, population-based study among elderly patients has found that current hypertension and hypertension established more than 5 years previously are associated with WMLs in the subcortical and periventricular regions.[17] Furthermore high systolic blood pressure and high diastolic blood pressure is associated with WML progression.[18] This may explain

the increased prevalence of WMLs (65.1% vs 32.3%) in women with chronic hypertension compared to those women who were normotensive.

Twelve out of 17 women whose blood pressure had normalised after delivery showed regression of lesions. Studies in the ageing population particularly patients with long-standing chronic hypertension have not shown any regression of lesions. There are however studies that have shown that in acute conditions of severe pre-eclampsia and eclampsia the clinical findings and radiologic abnormalities occurring in PRES resolve almost completely after restoration of normal blood pressure.[6,8] Similarly, a case-report of 2 non-pregnant adults and a child with hypertensive encephalopathy reported reversal of WMLs 4-5 weeks after initial studies.[34] The authors of this case-report stated that hypertensive encephalopathy is caused by multifocal extravasation of fluid and proteins across the blood-brain barrier during break-through of cerebral autoregulation.[34] Furthermore the high-intensity lesions seen on MRI are reflections of this protein and fluid extravasation and that resolution of lesions reflect their reabsorption.[34] This may explain the regression of some lesions in our study, particularly those in the occipital regions which may suggest that lesions in the occipital lobes are the consequence of PRES.

The strength of this study was that this is the first paper to show that in women with severe pre-eclampsia, WMLs most likely develop during the ante-natal period and that lesions that persist are unlikely the consequence of PRES. A possible limitation of the study is that most patients were seen for the first time during pregnancy with severe acute hypertension. Only 14.9% of women were known with chronic hypertension. It is possible that some women had undiagnosed chronic hypertension – this is especially likely as the rate of chronic hypertension postpartum was 61%. A further limitation of the study is that only a select group of pre-eclamptic patients were recruited to the study and relation between the WMLs and neurocognitive function was not evaluated.

3.5 CONCLUSION

Women who develop pre-eclampsia during pregnancy have an increased risk of developing cerebral white matter lesions after delivery. This risk is further increased in women who require 2 or more drugs to control blood pressure during pregnancy and those who develop chronic hypertension after the pregnancy.

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CHAPTER 4

Cardiac diastolic function after recovery from pre-eclampsia

Background
Pre-eclampsia is associated with significant changes to the cardiovascular system during pregnancy. Eccentric and concentric remodelling of the left ventricle occurs resulting in impaired contractility and diastolic dysfunction. It is unclear whether these structural and functional changes resolve completely after delivery.

Aims and objectives
The objective of the study was to determine cardiac diastolic function at delivery and 1 year postpartum in women with severe pre-eclampsia and to further determine possible future cardiovascular risk.

Methods
This was a descriptive study performed at Steve Biko Academic Hospital, a tertiary referral hospital in Pretoria, South Africa. Ninety-six women with severe pre-eclampsia and 45 normotensive women with uncomplicated pregnancies were recruited during the delivery admission. Seventy-four (77.1%) women in the pre-eclamptic group were classified as a maternal near miss. Transthoracic doppler echocardiography was performed at delivery and 1 year post-partum.

Results
At 1 year postpartum, women with pre-eclampsia had a higher diastolic blood pressure (p=0.001) and body mass index (p=0.02) than women in the normotensive control group. Women with early onset pre-eclampsia requiring delivery prior to 34 weeks gestation had an increased risk of diastolic dysfunction at 1-year postpartum (RR 3.41, 95% CI 1.11-10.5, P=0.04) and this was irrespective of whether the patient had chronic hypertension or not.

Conclusion

Women who develop early onset pre-eclampsia requiring delivery before 34 weeks are at a significant risk of developing cardiac diastolic dysfunction 1-year after delivery compared to normotensive women with a history of a low-risk pregnancy.

4.1 INTRODUCTION

Pre-eclampsia is a pregnancy specific disorder characterised by new onset hypertension and proteinuria after 20 weeks gestation. Hypertensive disorders in pregnancy have been one of the top 5 causes of maternal mortality in South Africa for more than a decade.[1] It was previously believed that the complications of pre-eclampsia ended with the delivery of the fetus and placenta, however it is now well established that pre-eclampsia is a risk for future hypertension, ischemic heart disease, stroke and venous thromboembolism.[2]

Pregnancy is associated with significant hemodynamic and hormonal changes affecting the cardiovascular system. There is a 20% increase in cardiac output by 8 weeks gestation.[3] Peripheral vasodilatation leads to a 20-30% fall in systemic vascular resistance and a 40% increase in cardiac output. The heart undergoes remodelling with an increase in left ventricular wall thickness and mass.[4] Despite these changes the left ventricle contractile function is maintained and any changes in cardiac geometry are rapidly reversible within 3 months postpartum in normotensive women.[4] In contrast, vascular reactivity is augmented in pregnancies affected by pre-eclampsia.[5] Pre-eclampsia results in a state of increased vascular stiffness, generalised vasoconstriction and a high total vascular resistance and a low cardiac output compared to the changes seen in a normal pregnancy. [5]

Cardiac changes classically associated with pre-eclampsia are diastolic dysfunction and an after-load mediated left ventricular remodelling of the maternal heart.[6,7,8] The heart remodelling is a response to the increased systemic afterload in order to minimise myocardial oxygen demand and preserve left ventricular function. About 20% of women with preterm pre-eclampsia and severe disease undergo severe left ventricular hypertrophy with advanced cardiac dysfunction.[9] Typically there is preservation of both left

atrial geometry and function and left ventricular systolic function.[10,4] The right ventricle is also usually unaffected.[10]Levels of brain naturetic peptide (BNP) increase in pregnancies complicated by pre-eclampsia and Fayers et al have shown that the increase in BNP is accompanied by changes in left ventricular diastolic function.[11] Elevated BNP levels are possibly the result of myocardial remodelling and sub-clinical ventricular dysfunction that accompanies the severe vasoconstriction observed in pre-eclampsia.[11]

Diastolic dysfunction is described as impaired left ventricular filling and may be present in the setting of normal or abnormal systolic function. Pre-clinical diastolic dysfunction is associated with the development of future heart failure and is a predictor of all-cause mortality.[12]Diastolic filling abnormalities may also play a significant role in the pathogenesis of pulmonary oedema complicating hypertensive crises in pregnancy.[13] Desai et al found that diastolic filling abnormalities were demonstrated in a significant proportion of pre-eclamptic pregnancies complicated by pulmonary oedema compared to control groups of women who were hypertensive and normotensive in pregnancy.[13] The authors of this study postulated that the diastolic filling abnormalities demonstrated in the study occurred within a short time frame of severe pre-eclampsia in pregnancy or could represent pre-eclampsia superimposed on established hypertension. Whether diastolic dysfunction persists after delivery is uncertain. Identifying factors which may affect future cardiovascular risk may identify a group of women requiring increased postpartum vigilance and life-style modification. The aim of this study was to determine cardiac diastolic function at delivery and 1 year postpartum in women with severe pre-eclampsia and to further determine possible future cardiovascular risk.

4.2 METHODS

This was a descriptive study of women with severe pre-eclampsia performed at Steve Biko Academic Hospital from 1 April 2013 to 30 March 2016. The Cardiology Department at Steve Biko Academic Hospital reserved echocardiographic appointments every Wednesday during the study period. Post-partum women with severe pre-eclampsia were identified on a Wednesday morning and if fit to be transported to the cardiology clinic were informed of the study. Echocardiographic studies performed on patients who consented to the procedure and were agreeable to follow-up studies. One hundred and six women with severe pre-eclampsia and 45 normotensive, low-risk women who served as the control group were identified and recruited shortly after delivery. Women with structural heart disease or pulmonary embolus were excluded from the study. Women diagnosed with maternal metabolic syndrome were not recruited to the control group. Echocardiograms of the maternal heart were performed between day 2-7 post-delivery and follow-up scans were done after 1 year. Hypertensive disorders were classified according to the classification and diagnosis of the International Society for the Study of Hypertension in Pregnancy (ISSHP).[14]

Doppler echocardiography was carried out by the Department of Cardiology at Steve Biko Academic Hospital. The following echocardiographic parameters were assessed in the evaluation of diastolic dysfunction: left ventricular ejection fraction (LVEF), the mitral E-wave velocity (E) and mitral A -wave velocities (A), the E/A ratio, the mitral E-velocity deceleration time (DT), lateral early diastolic (e') velocity tissue doppler and E/e' ratio. The diagnosis of diastolic dysfunction was made by a clinician in the cardiac-obstetric unit. All women diagnosed with diastolic dysfunction had the following minimum positive criteria: average E/e' > 14 and lateral e' velocity < 10cm/s. The American Society of Echocardiography and the European Association of Cardiovascular Imaging have described the advantages and limitations used to assess left ventricular diastolic function.[15] (Table 1)

4.2.1 Table 1 Utility, advantages and limitations of variables used to assess LV diastolic function[15] (reproduced with permission)

Variable	Physiologic background	Advantages	Limitations
Mitral E velocity	Reflects the LA-LV pressure gradient during early diastole and is affected by alterations in the rate of LV relaxation and LAP	Feasible and reproducible	Directly affected by alterations in LV volumes and elastic recoil Age dependent
Mitral A velocity	Reflects the LA-LV pressure gradient during late diastole, which is affected by LV compliance and LA contractile function	Feasible and reproducible	Sinus tachycardia, first-degree AV block and paced rhythm can result in fusion of the E and A waves. If mitral flow velocity at the start of the atrial contraction is >20cm/sec, A velocity may be increased Age dependent
Mitral E/A ratio	Mitral inflow E/A ratio and DT are used to identify the filling patterns	Feasible and reproducible Provides diagnostic and prognostic information A restrictive filling	The U-shaped relation with LV diastolic function makes it difficult to differentiate normal from PN

		pattern in combination with LA dilatation in patients with normal EFs is associated with a poor prognosis similar to a restrictive pattern in dilated cardiomyopathy	filling, particularly with normal LVEF, without additional variables If mitral flow velocity at the start of atrial contraction is > 20cm/sec, E/A ratio will be reduced due to fusion Age dependent
Mitral E-velocity DT	DT is influenced by LV relaxation, LV diastolic pressures following mitral valve opening, and LV stiffness	Feasible and reproducible A short DT in patients with reduced LVEFs indicates increased LVEDP with high accuracy both in sinus rhythm and in AF	DT does not relate to LVEDP in normal LVEF Should not be measured with E and A fusion due to potential inaccuracy Age dependent
Pulsed wave TDI-derived mitral annular early diastolic velocity: e'	A significant association is present between e' and the time constant of LV relaxation shown in both animals and humans The hemodynamic	Feasible and reproducible LV filling pressures have a minimal effect on e' in the presence of impaired LV relaxation Less load	Need to sample at least two sites with precise location and adequate size of sample volume Different cut-off values depending on the sampling

	determinants of e' velocity include LV relaxation, restoring forces and filling pressure	dependent than conventional blood-pool Doppler parameters	site for measurement Age dependent
Mitral E/e' ratio	e' velocity can be used to correct for the effect of LV relaxation on mitral E velocity, and E/e' ratio can be used to predict LV filling pressures	Feasible and reproducible Values for average E/e' ratio < 8 usually indicate normal LV filling pressures, values > 14 have high specificity for increased LV filling pressures	E/e' ratio is not accurate in normal subjects, patients with heavy annular calcification, mitral valve and pericardial disease "Gray zone" of values in which LV filling pressures are indeterminate Different cut-off values depending on the sampling site for measurement

Descriptive statistics in the form of means and standard deviations in the case of continuous data and frequencies and percentages in the case of categorical data was calculated. A p-value of < 0.05 was considered significant. Ethical approval for the study was obtained from the University of Pretoria Ethics Committee (No. 125/2013).

4.3 RESULTS

There were 6 536 deliveries at our hospital during the recruitment phase of the study (1 April 2013 – 30 March 2015). Four hundred and sixty-three (7.1%) women presented with severe pre-eclampsia and 106 women were recruited to the study. Ten women were lost to follow-up. Data was therefore recorded for 96 women with severe pre-eclampsia and 45 controls. Seventy-four (77.1%) women in the study group for whom data was available fulfilled the World Health Organisation (WHO) criteria for the classification of a maternal near miss. Of the 96 women with severe pre-eclampsia 14 were diagnosed with chronic hypertension and 4 were diagnosed with diabetes prior to pregnancy. At 1-year the mean diastolic blood pressure and mean body mass index was significantly higher among the women who had pre-sclampsia during pregnancy compared to the normotensive control group. Table 2 describes the demographic data of the study population.

4.3.1 Table 2 Demographic data of the study population

Characteristics	Pre-eclamptic group (n=96)	Control group (n=45)	p-value
Age, years			
Mean (SD)	28,9 (6.83)	27,2 (7.14)	0.66
Range	18-46	20-42	
Race			
African, n (%)	86 (89.58%)	38 (84.44%)	
Caucasian, n (%)	5 (5.20%)	3 (6.67%)	
Coloured, n (%)	4 (4.17%)	4 (8.89%)	
Indian, n (%)	1 (1.04%)	0 (0%)	
Obstetric History			
Parity mean (range)	1.3 (0-4)	1.6 (0-5)	
Timing of delivery			
< 34 weeks, n (%)	44 (45.83%)	0 (0%)	

34-37 weeks, n (%)	25 (26.04%)	5 (11.11%)	
>37 weeks, n (%)	27 (28.13%)	40 (88.89%)	
Medical conditions			
Diabetic at 1 year, n (%)	6 (6.25%)	0 (0%)	
Hypertensive at 1 year, n (%)	52 (54.17%)	2 (4.44%)	
Haemoglobin at 1 year (g/dL)			
Mean (SD)	12,02 (1.46)	12,42 (1.13)	0.15
Blood pressure at 1 year (mmHg)			
Systolic, mean (SD)	128.01 (14.17)	115.08 (9.89)	0.08
Diastolic, mean (SD)	80.91 (14.47)	72.45 (9.16)	**0.001**
BMI at 1 year, mean (SD)	30.27 (7.55)	28.04 (3.64)	**0.02**

Twenty women (20.83%) with pre-eclampsia were diagnosed with diastolic dysfunction at delivery compared with six (13.3%) of the controls (p = 0.26). Of the 20 women who were diagnosed with diastolic dysfunction at delivery, 13 (65%) women had early onset pre-eclampsia requiring delivery prior to 34 weeks. At 1-year, eleven (11.46%) women with pre-eclampsia were diagnosed with diastolic dysfunction compared with 3 (6.67%) in the control group. (RR = 1.67; p = 0.27). Women with early onset pre-eclampsia requiring delivery prior to 34 weeks gestation had an increased risk of diastolic dysfunction at 1-year postpartum (RR 3.41, 95% CI 1.11-10.5, P=0.04). (Figure 1) Delivery < 34 weeks was associated with an increased risk of diastolic dysfunction even if patients with chronic hypertension at 1 year were excluded from the analysis. (p=0.02, 95% CI 1.43 – 97.67) There was no significant association between diastolic dysfunction and chronic hypertension at 1 year (RR = 2.02, p = 0.33, 95% CI = 0.57-7.13).

4.3.2 Figure 1 Risk of diastolic dysfunction at delivery, 1-year and 1-year for sub-group of women with early onset pre-eclampsia requiring delivery < 34 weeks.

Echocardiographic measurements of diastolic function after 1-year are shown in Table 3. The left ventricular systolic function was normal and similar in both groups suggesting preservation of systolic function in pre-eclamptics and controls. There was a significant decrease in lateral e' and significant increase in the A velocity between the pre-eclamptic and control group at 1-year.

4.3.3 Table 3 Cardiac diastolic function at 1 year

	Pre-eclamptic group, Mean (SD)	Control group, Mean (SD)	p-value
Left ventricular ejection fraction, %	60.54 (7.62)	63.43 (4.88)	0.08
E velocity, m/s	0.98 (0.20)	0.95 (0.14)	0.90
A velocity, m/s	0.70 (0.24)	0.64 (0.05)	**0.01**
E/A ratio	1.42 (0.39)	1.46 (0.12)	0.74
E-deceleration time (ms)	224.57 (51.00)	225.43 (35.09)	0.08
Lateral e' (cm/second)	10.83 (2.86)	11.80 (1.99)	**0.02**
E/e' ratio	10.11 (5.32)	9.96 (2.25)	0.11

4.4 DISCUSSION

Heart failure is a progressive condition which begins with risk factors for left ventricular dysfunction and progresses further to asymptomatic changes in cardiac structure and function and finally evolves into heart failure.[16] Myocardial remodelling starts before the onset of symptoms. Diastolic dysfunction precedes the onset of systolic dysfunction in 50% of cardiac diseases which further precedes the onset of heart failure.[5] The American College of Cardiology has highlighted the importance of identifying asymptomatic cardiac dysfunction for early intervention and improvement of outcome.[17] The risk for left ventricular diastolic dysfunction is significantly associated with higher age, body mass index, heart rate and systolic blood pressure.[16] The prevalence of diastolic dysfunction in a general population aged less than 49 years was found to be 6.8% and 27.3% for the total population which included study subjects older than 70 years.[16] Zanstra et al found that 24% of women with a metabolic syndrome during pregnancy had diastolic dysfunction at 6 months postpartum compared to 6.3% of women with low risk pregnancies.[18] Obesity and diastolic hypertension were strong correlates to diastolic dysfunction. The rate of diastolic dysfunction at 1 – year in the 2 groups of women with early onset pre-eclampsia (22.7%) and low risk pregnancies (6.7%) in our study were similar to rates reported by Zanstra et al.[16] Although our study did not find associations between diastolic blood pressure and obesity with diastolic dysfunction, women in the pre-eclamptic group had a significantly higher BMI and diastolic blood pressure than those in the control group. Additionally, diastolic dysfunction is also a risk factor for future death. The Olmsted study described the predictive significance of left ventricular diastolic dysfunction using multivariable-adjusted analyses.[19] The hazard ratio for all-cause mortality was 8.31 ($p<0.001$) for mild diastolic dysfunction and 10.17 for moderate to severe diastolic dysfunction ($P<0.001$).

At 1-year post- delivery diastolic dysfunction was present in 11.5% of women with pre-eclampsia, in 22.7% of women with early onset pre-eclampsia and

1.9% of women who pre-eclampsia developed after 34 weeks. Women with early onset pre-eclampsia requiring delivery prior to 34 weeks, irrespective of the presence chronic hypertension, are at risk of developing diastolic dysfunction at one year post-delivery. Chronic hypertension, therefore, was not an additional risk factor diastolic dysfunction at 1- year in women with early onset pre-eclampsia. This study has found that early onset pre-eclampsia is a risk factor for diastolic dysfunction while women who develop pre-eclampsia after 34 weeks have a risk similar to that of low-risk parous women (RR 3.41, 95% CI 1.11-10.5, P=0.04). This may be explained by the proposed differences in pathophysiology between early and late-onset pre-eclampsia. Redman et al have suggested that pre-eclampsia could be the result of intrinsic or extrinsic placental causes.[20] In early-onset pre-eclampsia factors extrinsic to the placenta affect the uteroplacental circulation via incomplete spiral artery remodelling while in late-onset disease intrinsic factors affect the size of the placenta restricting intervillous perfusion.[20] The placentas of women with early onset disease differ significantly with those women who develop pre-eclampsia at term.[21] The former group demonstrate placental findings consistent with insufficiency and vascular lesions while late onset disease is characterised by placental hyperplasia and unimpaired fetal growth.[21, 22, 23,24] Further evidence suggesting that pre-eclampsia is more than one disease comes from differences in biochemical markers, doppler studies and clinical features of the disease.[25,26,27,28,29,30]

Pre-eclampsia is a known risk factor for future chronic hypertension. Hypertension and hypertensive heart disease are one of the key contributors to the burden of non-communicable cardiovascular disease in Africa. Young African women are bearing the brunt of this increasing public health problem.[31,32] Several studies have found that women from sub-Saharan Africa have the greatest risk of developing pre-eclampsia and eclampsia. [33,34] Nakimuli et al, in a study of preecampsia in women of African ancestry, found that African ancestry was the second strongest risk factor for pre-eclampsia after chronic hypertension.[35] African ancestry was also a risk factor for early onset

pre-eclampsia and poor obstetric outcomes such as fetal growth restriction and stillbirth.[35] Pregnancy-related deaths from pre-eclampsia are also 3 times higher in women of African ancestry compared with Europeans.[36] Almost 90% of women in our study were of African origin. It is estimated that for every women who dies during pregnancy or childbirth, 20 others will suffer severe morbidity.[37] Most maternal mortality and morbidity data sets record information for up to 42 days postpartum. However women who develop pre-eclampsia during pregnancy, especially those with early onset disease may develop heart failure several years after pregnancy resulting in the problem not being adequately identified and addressed.

The prognosis of women with compromised cardiac function is poorer than that of men.[18] Women often present with atypical symptoms resulting in delayed presentation, delayed diagnosis and suboptimal care compared to men.[38,39] These factors highlight the need to identify women at risk of future cardiovascular disease with the aim of reducing potential modifiable risk factors. Blood pressure control, weight loss and a low sodium diet are important measures that have been identified with favourable changes in ventricular diastolic function.[18] The American Heart Association Guideline on Lifestyle Management to reduce cardiovascular risk for adults who would benefit from blood pressure lowering include dietary modification appropriate to calorie requirements, reduction in salt intake and 3-4 sessions of aerobic activity per week lasting on average 40 minutes per session.[40]

This is the first study to evaluate diastolic function in a pre-eclamptic group of predominantly African population. Although we did not look at other risk factors for cardiovascular disease in this population, the study provides valuable information in identifying a potential group of women at risk of disease at an early stage. This would provide opportunities for screening and life-style modification.

The strength of this study is that it is one of the first to look at cardiac diastolic function in an African population where the rates of hypertension both during and outside of pregnancy are high. A possible limitation is that most patients were seen for the first time during pregnancy with severe acute hypertension. Only 14.6% of women were known with chronic hypertension. It is possible that some women had undiagnosed chronic hypertension – this is especially likely as the rate of chronic hypertension postpartum at 1 year was 54.2%. Some of the women with undiagnosed chronic hypertension may have had pre-existing diastolic dysfunction that could have worsened by the superimposed pre-eclampsia. A further limitation is that only a select group of pre-eclamptic women were recruited to the study.

4.5 CONCLUSION

Women who develop early onset pre-eclampsia requiring delivery prior to 34 weeks gestation have an increased risk of cardiac diastolic dysfunction 1 year after delivery. Diastolic dysfunction precedes the onset of systolic dysfunction and clinical heart failure. A strategy to screen and treat women with cardiovascular risk, particularly in lower- and middle income countries should be explored further.

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CHAPTER 5

The effect of pre-eclampsia on retinal microvascular caliber at delivery and post-partum: a case-control study

Background
Pre-eclampsia is a pregnancy specific disorder which contributes to gross maternal vascular dysfunction. Women with a history of pre-eclampsia are more likely to develop long-term hypertension and cardiovascular disease. The retinal microcirculation provides a unique view of microvessel structure by means of non-invasive, retinal image analysis.

Objectives
To compare the retinal vessel caliber at delivery and 1-year post-partum between women who have had pre-eclampsia during pregnancy to a normotensive control group.

Methods
This was a case control study at a tertiary referral hospital in Pretoria, South Africa. The study group comprised of 40 women with severe pre-eclampsia and 40 normotensive women. Digital photos of the eye were taken at delivery and 1-year post-partum. Retinal vessels were analysed and summarised as the central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE). The CRAE and CRVE were corrected for mean arterial blood pressure to produce the corrected central retinal arteriolar equivalent (cCRAE) and corrected central retinal venular equivalent (cCRVE).

Results
The cCRAE and cCRVE were significantly lower in the pre-eclamptic group compared to the control group both at delivery and 1-year post-partum ($p < 0.001$). Although there was an increase in cCRAE and cCRVE between delivery and 1-year in the pre-eclamptic and control groups, these increases were not significant.

Conclusion

Retinal artery and venular caliber changes that occur during pregnancies affected by pre-eclampsia persist for up to 1 year post-partum. These changes may reflect a permanent, long-term microvascular dysfunction and may be useful as a biomarker of future vascular risk.

5.1 INTRODUCTION

Pre-eclampsia is a pregnancy specific disorder characterised by new onset hypertension after 20 weeks gestation. Although the pathogenesis of pre-eclampsia is still poorly understood, it is well recognised that the disease contributes to gross maternal vascular dysfunction.[1] Endothelial dysfunction, resulting in increased peripheral resistance, is an integral part of the maternal syndrome. The ischemic placenta releases a number of pro- and anti-angiogenic factors and inflammatory markers into the maternal circulation. These factors are critical in mediating vascular function.[2] Vessels of women with pre-eclampsia show hypersensitivity to vasopressors and decreased response to vasodilators and vascular levels of vasodilators such as nitric oxide and prostacyclin are reduced in women with pre-eclampsia.[2,3,4,5,6]

The degree of dilatation and constriction of the retinal microvasculature during normal pregnancy have been shown to correlate with the physiological changes in the mean arterial blood pressure.[7] Differences in retinal microvasculature are believed to reflect cerebrovascular changes and are associated with systemic changes in vascular response.[8] The retinal microcirculation provides a unique view of microvessel structure by means of non-invasive, image analysis.[8] Retinal imaging primarily measures retinal microvessel caliber and retinal vessel caliber is relatively stable in healthy individuals with only subtle constriction for each decade increase in age.[9]

Lupton et al compared the changes in retinal microvessel caliber during pregnancy between women who had a normotensive pregnancy to those who subsequently developed pre-eclampsia.[10] The central retinal arteriolar equivalent corrected for mean blood pressure (cCRAE) was significantly lower at term in the pre-eclamptic group compared to women who were normotensive during pregnancy. In general populations, such narrowing of retinal arteriolar caliber has been associated with increased risk of severe

hypertension and stroke.[11,12] However it is uncertain whether changes in retinal arteriolar vessel caliber during pregnancies complicated by pre-eclampsia recover after delivery of the fetus and placenta or persist beyond the immediate post-partum period and whether such changes may be markers of future risk. There have been studies showing that women with a history of pre-eclampsia are more likely to develop hypertension and cardiovascular disease in later life.[13,14]

The aim of this study was to compare the retinal vessel caliber at delivery and 1-year post-partum between women who have had pre-eclampsia during pregnancy to a normotensive control group.

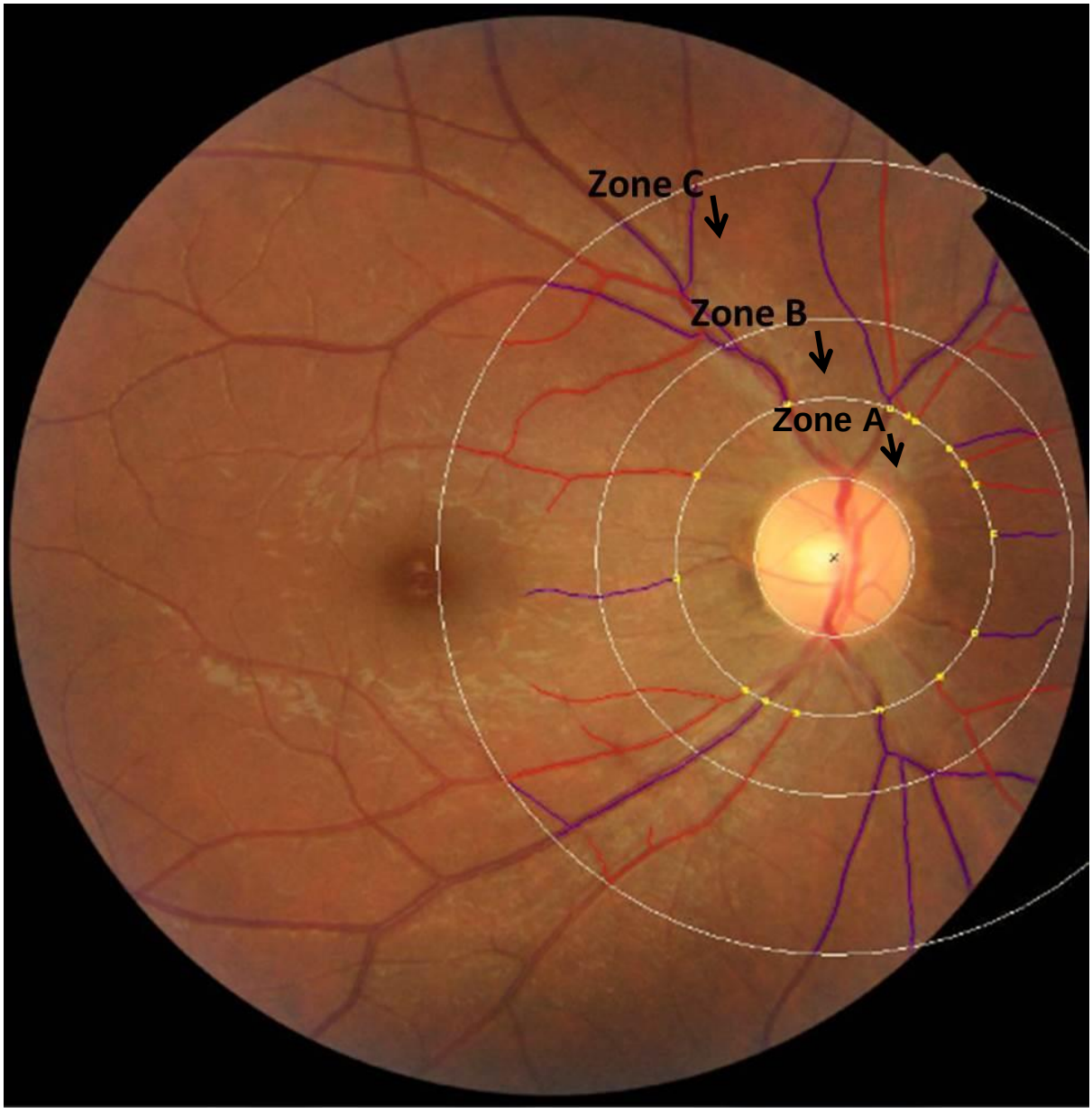
5.2 METHODS

This was a case-control study of women with severe pre-eclampsia at Steve Biko Academic Hospital, a tertiary referral hospital in Pretoria South Africa, from 1 April 2013 – 30 March 2016. This study formed part of a larger study of pre-eclamptic women which included the evaluation of cardiac diastolic function using echocardiography and the investigation for the presence of cerebral white matter lesions (WMLs) by magnetic resonance imaging (MRI). Recruitment of patients took place from 1 April 2013 – 30 March 2015 and follow-up visits took place from 1 April 2014 – 30 March 2016. Post-partum women (day 2-7 post-delivery) with severe pre-eclampsia were identified every morning during the labour ward round. Women were informed of the study if they were fit to be transported to various departments in the hospital for imaging studies. Retinal images were collected at delivery and 1 year post-partum in patients who also consented to undergoing echocardiography and MRI imaging at delivery and were agreeable to follow-up visits. Normotensive women who had uncomplicated pregnancies served as the control group. Hypertensive disorders were classified according to the classification and

diagnosis of the International Society for the Study of Hypertension in Pregnancy (ISSHP).[15]

Retinal imaging was performed using the Topcon TRC-NW8 45^0 non-mydriatic retinal fundus camera. Photographs were taken between day 2-7 post-delivery and at 1 year post-partum. Women were rested for a few minutes in a dark room before photography to achieve pupil dilatation without pharmacological mydriasis. Macula-centred digital photographs of both fundi were taken. The right eye was chosen for analysis because retinal vessel characteristics are comparable between the right and left eyes.[16] Photographs were graded at the Singapore Eye Research Institute. Retinal image graders were blinded to the clinical information of the study patients. Images were graded using a semi-automated retinal vascular caliber measurement software program which identified all retinal vessels that passed through an area between ½ and 1 disc diameter from the optic disc margin (zone B) (Figure 1) and measured the caliber of the arterioles and venules.[17] Retinal vascular caliber was assessed using a standardised protocol based on the revised Knudtson-Parr-Hubbard formula.[18] Retinal arteriolar and venular calibers were summarised using the 6 largest arterioles and the 6 largest venules as the central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE) respectively.

5.2.1 Figure 1 Digitized retinal photograph. Zone B is a half-disc to one and half disc diameter from the optic disc margin. Retinal vessel diameter measurements were performed in Zone B.



The mean arterial blood pressure (MAP) was calculated using the formula MAP=DP+1/3(SP-DP), where DP and SP represent systolic and diastolic blood pressure respectively. The effect of blood pressure on retinal vessel caliber was corrected by dividing the CRAE and CRVE by the MAP to produce the corrected CRAE (cCRAE) and corrected CRVE (cCRVE) respectively.[19] Descriptive statistics in the form of means and standard deviations was performed. Univariate

analysis comparing women with pre-eclampsia and the control group at delivery then 1 year were performed making use of independent sample t-tests. A p-value of < 0.05 was considered statistically significant. Ethical approval for the study was obtained from the University of Pretoria Research Ethics Committee (No. 125/2013).

5.3 RESULTS

There were 6 536 deliveries at Steve Biko Academic Hospital during the recruitment phase of the study (1 April 2013 – 30 March 2015). Four hundred and sixty-three (7.1%) women presented with severe pre-eclampsia and 106 women were recruited to the larger study (described in methods). Seven women were lost to follow-up and five declined testing at different stages of the study. Data was therefore available for 94 patients. Seventy-three (77.7%) women for whom data was available fulfilled the World Health Organisation (WHO) criteria for the classification of a maternal near miss.[20] Research funding was available for grading of 160 digital photographs. Forty pairs of the best quality digital fundus photographs, at delivery and 1-year post-partum, were selected from the pre-eclamptic and control study groups for grading at the Singapore Eye Research Institute. Fifty-five percent (n= 22) of women in the pre-eclamptic group were diagnosed with chronic hypertension at 1-year. There was a statistically significant difference in the mean arterial blood pressure between the pre-eclamptic and control groups at delivery and 1-year ($p < 0.001$). The demographic data of the study population is described in Table 1.

5.3.1 Table 1. Demographic data of the study population

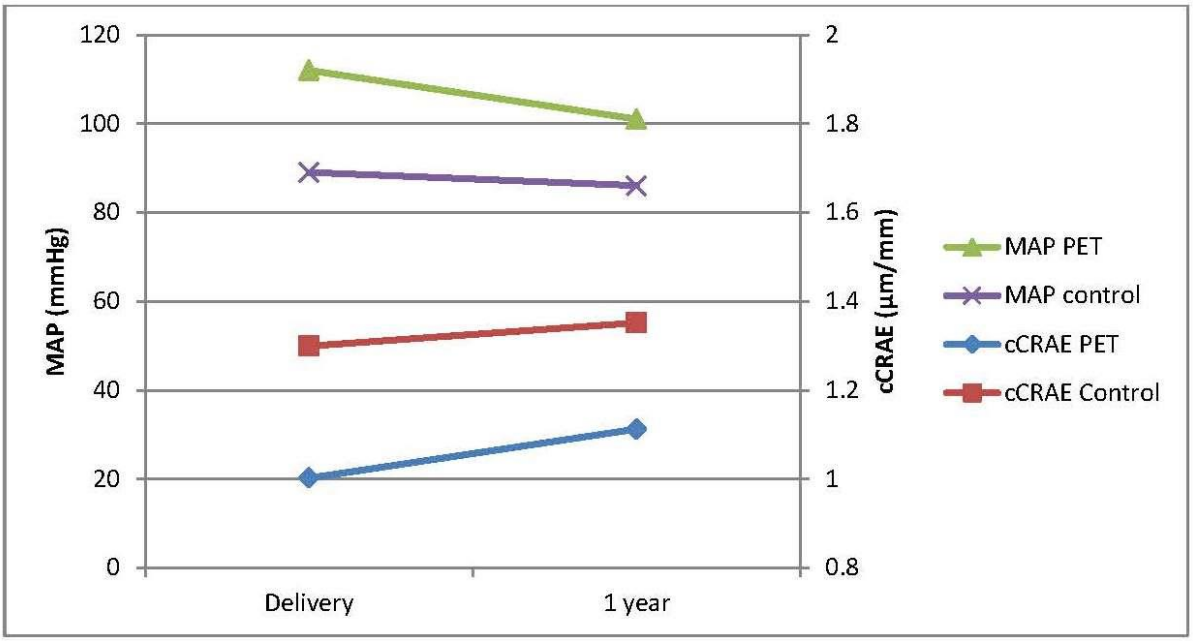
	Pre-eclamptic group (n=40)	Control group (N=40)
Age, years		
Mean (SD)	29.3 (6.4)	29.1 (7.5)
Range	17-41	18-46
Race		
African, n (%)	35 (87.5)	35 (87.5)
Caucasian, n (%)	2 (5.0)	3 (7.5)
Coloured, n (%)	2 (5.0)	2 (5.0)
Indian, n (%)	1 (2.5)	0
Timing of delivery		
< 34 weeks, n (%)	25 (62.5)	0
>34 weeks, n (%)	15 (37.5)	40 (100.0)
Mean birth weight		
Grams, (SD)	1893 (842.1)	3192 (342.8)
Medical Conditions		
Diabetic at 1 year, n (%)	2 (5.0)	0
Hypertensive at 1 year, n (%)	22 (55.0)	1 (2.5)
MAP(mmHg) at delivery mean (SD)	111.73 (7.52)	88.78 (7.44)
MAP(mmHg) at 1-year mean (SD)	100.50 (15.22)	89.92 (7.88)

The mean cCRAE and cCRVE was significantly lower in the pre-eclamptic group compared with the control group both at delivery and 1 year. (Table 2) There was a 0.30µm and 0.24µm difference in cCRAE between the pre-eclamptic and control groups at delivery and 1-year respectively. The difference in cCRVE between the 2 groups at delivery was 0.36µm and 0.31µm at 1-year. There was a non-significant increase of 0.11µm (p=0.10) in the cCRAE between delivery and 1-year in the pre-eclamptic group. This correlated with a decrease in the MAP between the 2 time-periods. (Figure2a+b) The increase of 0.19µm in the cCRVE in the pre-eclamptic group between delivery and 1-year was statistically significant (p=0.02).

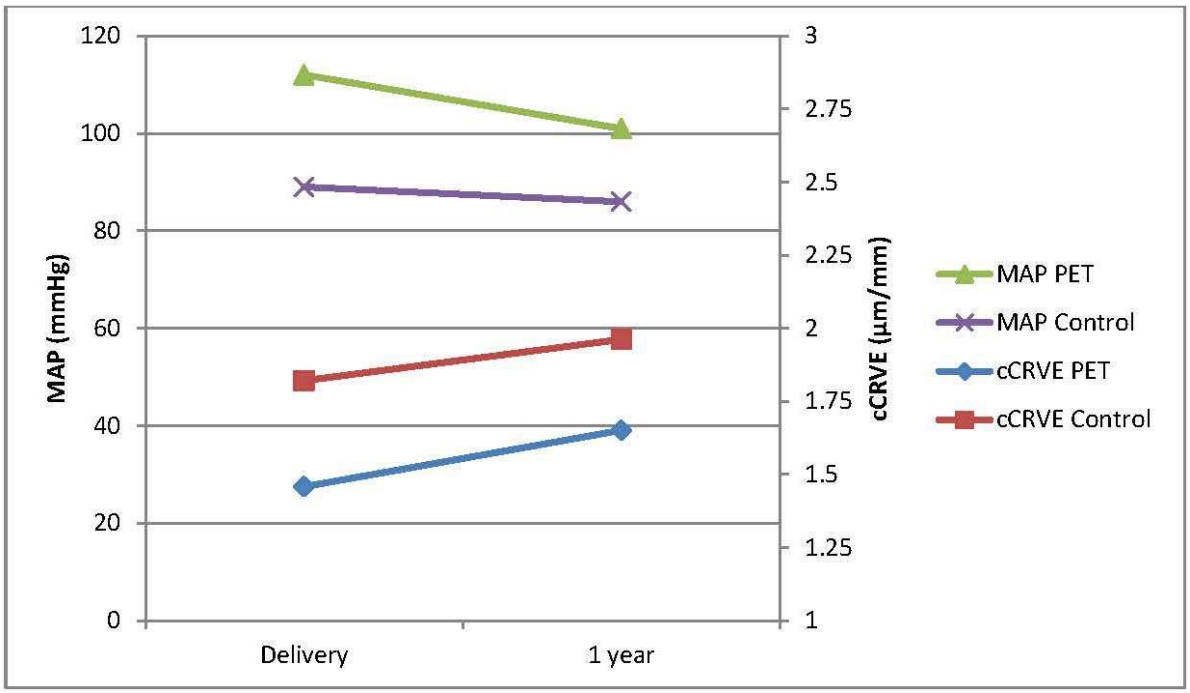
5.3.2 Table 2. Comparison between the retinal artery and vein caliber between the pre-eclamptic and control groups at delivery and 1-year

	Pre-eclamptic group (n=40)	Control group (n=40)	p-value
Delivery			
MAP (mmHG) Mean (SD)	111.73 (7.52)	88.76 (7.44)	P < 0.001
cCRAE(µm) mean (SD)	1.00 (0.15)	1.30 (0.21)	P < 0.001
cCRVE(µm) mean (SD)	1.46 (0.15)	1.82 (0.38)	P < 0.001
1-year Post-partum			
MAP (mmHG) Mean (SD)	100,50 (15.22)	85.92 (7.89)	P < 0.001
cCRAE(µm) mean (SD)	1.11 (0.22)	1.35 (0.26)	P < 0.001
cCRVE(µm) mean (SD)	1.65 (0.36)	1.96 (0.30)	P < 0.001

5.3.3 Figure 2a Comparison of cCRAE between the pre-eclamptic group and control group showing the relation with MAP



5.3.4 Figure 2b Comparison of cCRVE between the pre-eclamptic group and control group showing the relation with MAP



Sixty percent of women in the pre-eclamptic group developed early onset pre-eclampsia requiring delivery before 34 weeks. A sub-analysis of this pre-eclamptic group showed that these women had an increased risk of developing diastolic dysfunction 1-year after delivery. Table 3 compares the cCRAE and cCRVE of the pre-eclamptic group at 1-year to various clinical sub-groups within the group of women with pre-eclampsia. Although the cCRAE and cCRVE at 1-year were smaller in women with early onset pre-eclampsia requiring delivery < 34 weeks and for pre-eclamptic women with chronic hypertension at 1-year, these differences were not significant. These non-significant findings are possibly due to the small study numbers within the sub-group of pre-eclamptic women.

5.3.5 Table 3. Comparison of cCRAE and cCRVE at 1-year between the women with pre-eclampsia and the different clinical sub-groups of women with pre-eclampsia

	cCRAE (μm) at 1 year, mean (SD)	p-value	cCRVE	p-value
Pre-eclamptic group n=40	1.11 (0.22)		1.65 (0.36)	
Early onset pre-eclampsia <34 weeks n = 24	1.08 (0.23)	0.52	1.57 (0.39)	0.38
Pre-eclamptic women with diastolic dysfunction at 1 year n = 5	1.14 (0.29)	0.77	1.64 (0.41)	0.94
Pre-eclamptic women with WMLs at 1-year n = 17	1.15 (0.24)	0.59	1.74 (0.32)	0.41
Pre-eclamptic women with hypertension at 1-year n = 22	1.04 (0.17)	0.19	1.48 (0.29)	0.06

5.4 DISCUSSION

Narrower retinal microvessel caliber seen in women with pre-eclampsia during pregnancy compared to a normotensive control group was first described by Lupton et al.[7,10] Ours is the first study to demonstrate that such retinal arteriolar and venular narrowing in women with pre-eclampsia during pregnancy persists for up to 1-year post-partum. Our study demonstrates longer-term effects of pre-eclampsia on the microvasculature and may provide insights into the higher risks of cardiovascular disease in women with a history of pre-eclampsia.

Vascular endothelial dysfunction is recognised as the key disturbance in the pre-eclamptic disease process. Anti-angiogenic factors such as tyrosine kinase receptor-1 (sFlt-1) are released by the placentas of women with pre-eclampsia. sFLT-1 is secreted into the maternal circulation and has an antagonistic effect on vascular endothelial growth factor (VEGF) and placental growth factor

(PIGF). VEGF and PLGF play important roles in maintaining the vascular endothelium and decreased VEGF levels further decrease nitric oxide synthesis resulting in a negative vasodilatory effect. VEGF is also responsible for inducing and maintaining the integrity of fenestrated endothelium in various tissues including the renal glomerulus, and VEGF blockade by sFLT-1 may be a cause for renal damage and a decrease in renal function.[21] Although many of the clinical manifestations of pre-eclampsia resolve after delivery, endothelial dysfunction may persist postpartum.[22] Chambers et al demonstrated that flow mediated dilatation is reduced in women with previous pre-eclampsia compared with uncomplicated pregnancies at a median interval of 3 years postpartum.[23] Endothelial dysfunction has been reported in other studies up to 27 months postpartum.[24,25,26] The mechanisms associated with the failure of blood vessels to maximally dilate include, endothelial dysfunction, a decrease in nitric oxide release, increased responsiveness to the pressor effect of angiotensin II and vasospasm.[23,27,28,29,30] There was a small increase in the cCRAE and cCRVE between delivery and 1-year in the pre-eclamptic group, however this increase was not significant. The sub-group of women who developed early onset pre-eclampsia requiring delivery before 34 weeks and those who developed chronic hypertension had a smaller cCRAE at 1-year than the combined group of women with pre-eclampsia.

Retinal vascular changes are markers of early pathogenic processes in hypertension and are related to both subclinical and clinical end-organ damage. The association between arteriolar narrowing and development of later hypertension has been described by Ding et al.[31] As a precursor of hypertension, increased peripheral resistance (similar to conditions like pre-eclampsia) occurs primarily in small arteries and arterioles. Therefore, arteriolar narrowing may contribute to an elevation in blood pressure, eventually leading to hypertension and a 'vicious cycle' may develop in which the microcirculation maintains or even amplifies an initial increase in blood pressure.[31,32] This pattern is also evident in women who develop pre-eclampsia where arteriolar narrowing precedes the clinical onset of hypertension during

pregnancy.[7] Retinal vessel caliber, during and after pregnancy, remains smaller in pre-eclamptic women than women who are normotensive during pregnancy and a proportion of women with pre-eclampsia during pregnancy will develop chronic hypertension. Fifty-five percent of women in our study remained hypertensive at 1-year. Previous studies have reported that arteriolar constriction and narrowing play a critical role in the earliest stages of hypertension development and retinal vessel wall signs have been associated with systemic markers of inflammation, confirming that inflammation plays a role in the development of hypertension.[33,34] In the Atherosclerosis Risk in Communities (ARIC) Study, normotensive persons aged 49 to 73 years with generalised or focal arteriolar narrowing were 60% more likely to develop hypertension within 3 years than persons without these signs, independent of vascular risk factors.[35] In a population-based cohort study, Smith et al found that generalised retinal arteriolar narrowing was significantly associated with 5-year incident severe (grade 2 or 3) hypertension, independent of other known risk factors for hypertension and baseline blood pressure status.[11] This association was stronger for younger (less than 65 years of age) participants.

The strong, consistent association between pre-eclampsia and future cardiovascular disease was shown in a meta-analysis by Bellamy and colleagues.[13] Coronary and retinal vessels undergo similar changes (such as sclerosis) in patients with hypertension.[36] Assessment of retinal vessels has been shown to correlate with coronary microvascular damage.[36,37] It has been hypothesised that microvascular disease may play a greater role in the development of myocardial ischemia and definite coronary heart disease in women than in men.[38,39] Wong et al found that retinal arteriolar narrowing is related to the risk of coronary heart disease in women but not in men.[40] In this study, every 1-SD decrease in the arteriole-to-venule ratio was associated with a 37% increase in coronary heart disease risk. Similarly, an individual-participant meta-analysis of 22 159 participants from 6 population-based studies has shown that microvascular dysfunction is a greater contributor and predictor of coronary heart disease in women than in men.[36]

In a meta-analysis of 198 252 women with pregnancies affected by pre-eclampsia, the relative risk for the development of stroke after 10 years was 1.81, 95% CI 1.45-2.27.[13] Retinal arteriolar narrowing and decreasing arteriole-to-venule ratio have been shown to predict incident stroke as well as MRI-identified subclinical stroke.[11, 12] The retinal and cerebral microvasculatures have been described as homologus.[41] Similar to changes in retinal vasculature, microvascular changes in the brain may lead to chronic ischemia and the development of white matter lesions. The disruption of the blood-brain barrier of the cerebral microcirculation is believed to be an important pathophysiological feature in the development of cognitive impairment and dementia.[42] Retinal vascular lesions are also believed to reflect a break-down of the blood-retinal barrier. Several studies have reported a relation between retinal vascular abnormalities and cognitive function.[43,44,45] In the hypertensive sub-group of the Cardiovascular Health Study, the presence of any retinopathy (OR 2.10, 95% CI 1.04-4.24) or focal arteriolar narrowing (OR 3.2, 95% CI 1.51-6.02) was associated with an increased risk of dementia.[44]

The detrimental effect of gestational hypertensive disorders on microvasculature is not limited to affected mothers only. Yessil et al have found that children of mothers with gestational hypertensive disorders had narrower retinal arteriolar calibers than children whose mothers were normotensive during their pregnancies.[46] It is believed that adverse fetal exposures linked with gestational hypertension during key vulnerable periods could be responsible in creating a permanent impact on microvascular development.[8] Early microvascular dysfunction is possibly responsible for the adverse hypertensive and cardiovascular profile observed in offspring of mothers who develop pre-eclampsia during pregnancy.

The strength of this study is that this is the first study to show that retinal vessel narrowing associated with pre-eclampsia persists in the post-partum period. The study is limited in that retinal vessel caliber was analysed in only a select group of patients from the larger study evaluating cardiac diastolic

function and cerebral white matter lesions after pre-eclampsia, and there were no pre-pregnancy readings of retinal vessel calibre. The smaller numbers means that a possible association between retinal vessel caliber, cerebral white matter lesions and diastolic dysfunction could not be determined accurately.

5.5 CONCLUSION

Retinal arteriolar and venular caliber changes that occur during pregnancies affected by pre-eclampsia persist for up to 1 year post-partum. These changes may be a reflection of permanent, long-term microvascular dysfunction in other organs systems and have been shown to be a predictor of future cardiovascular risk. Pre-eclampsia has a long-term negative effect on maternal health and strategies to prevent the development of pre-eclampsia should be explored further.

5.6 FUNDING

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CHAPTER 6

Quality of life one year after severe acute maternal morbidity: a descriptive study

Objectives
To compare the Quality of life (QoL) of women who were classified as a maternal near miss to a group of women who had an uncomplicated low-risk pregnancy

Methods
This was a descriptive study at a tertiary referral hospital in Pretoria, South Africa. Ninety-five maternal near misses were compared to 51control subjects who had a low risk pregnancy. QoL was assessed 1-year after delivery using the World Health Organisation Quality of Life questionnaire (WHOQOL-Bref). In addition women were asked about their desire for future fertility.

Results
One year after delivery, women who were classified as a maternal near-miss scored significantly lower than the control group on all 4 domains of the WHOQOL-Bref questionnaire ($p < 0.001$). Significantly more women in the control group had a desire for future fertility compared to women classified as a near-miss (82.4% vs 43.2%; $p < 0.001$). Near-miss women who suffered a perinatal loss scored significantly lower on domain scores for physical health and well-being, psychosocial health and well-being and the environment than those near miss women discharged home with a live baby, but near-miss women with a live baby still had significantly lower QoL scores than the control group.

Conclusion
A severe acute morbidity event in pregnancy reduces the desire for future reproduction and results in a poorer QoL when compared to women who have had uncomplicated pregnancies. A maternal near-miss event that is complicated by a perinatal loss results in an overall quality of life that is poorer than a near-miss event where a mother is discharged home with a live baby.

6.1 INTRODUCTION

A maternal near-miss refers to a woman who nearly died but survived a complication that occurred during pregnancy. Approximately 20 million acute complications of pregnancy occur globally every year.[1] There is little variation in the incidence of acute complications in pregnancy between developed and developing countries.[2] The difference in morbidity and mortality rates has been attributed to the way in which complications are detected and managed.[3] Women who suffer obstetric complications often suffer both immediate and long-term physical, social, financial and psychological consequences.[4] A significant proportion of morbidity events occurring during pregnancy are believed to be preventable, but the consequences constitute a public health expense with elevated financial and social costs.[5] Unfortunately health and support systems required to manage these complications are not always accessible to women in developing countries and in some countries the problem has not been recognised so no facilities are available.

The World Health Organisation (WHO) defines QoL as an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. QoL is a broad ranging concept affected in a complex way by the person's physical health, psychological state, level of dependence and social relationship to salient features of their environment.[6] Women who suffer from pre-eclampsia during pregnancy are at risk of developing chronic diseases such as hypertension and type 2 diabetes in future life.[7,8] A study of the health of women after severe obstetric complications found that this group of women remained at high risk and were at increased risk of dying, had worse mental-health outcomes, especially in terms of risk of depression in the first 3 months after birth and suicidal ideation.[9] Fillipi and colleagues found that although women who had severe obstetric complications sought post-partum care more often than women with uncomplicated deliveries, their need for care was not adequately met.[9] Women reported that they could not afford to seek care

when they needed it and in some cases they were able to consult with a health-care provider but were unable to buy the prescribed medication.

The aim of this study was to compare the QoL of women who were classified as a maternal near miss to a group of women who had an uncomplicated low-risk pregnancy.

6.2 METHODS

This was a descriptive study of maternal near-misses at Steve Biko Academic (SBAH), a tertiary referral hospital in Pretoria, South Africa from 1 April 2013 – 30 March 2016. SBAH is a referral hospital for the central and eastern Tshwane regions. Patient referrals are mainly from a level 1 hospital (Tshwane District Hospital) situated adjacent to SBAH and a level 2 hospital (Mamelodi Hospital) in Tshwane east. Very ill patients may be referred directly from midwife obstetric units in the referral area. Obstetric patients with underlying medical disease may be referred in from neighbouring provinces. Recruitment of patients took place from 1 April 2013 to 30 March 2015 and 1-year follow-up visits took place from 1 April 2014 to 30 March 2016. About 10% of deliveries at SBAH are low-risk. This is mainly the result of low-risk women presenting in labour for the first time.

One hundred and ten near-miss cases were prospectively identified at daily audit meetings at SBAH using the WHO criteria for a maternal near miss.[10] Fifty-five low risk women with uncomplicated pregnancies who delivered at SBAH were recruited to the control group. Both the near-miss and control groups of women were followed up for a post-natal visit one week after delivery. Near-miss patients were seen at the near-miss clinic monthly after delivery if they required chronic medication. All study patients (near-miss and control patients) were seen 1-year after delivery and were informed of the

purpose of the study and that their responses would remain confidential. The WHO quality of life (WHOQOL-Bref) assessment questionnaire was filled out during personal interviews by women who provided informed consent. The questionnaire was completed by female interviewers who were well versed in the local dialect if women were illiterate or did not speak the English language. The WHOQOL-Bref questionnaire contains 2 items assessing overall quality of life and general health, 7 items assessing physical health, 6 items assessing psychological health, 3 items assessing social relationships and 8 items assessing environmental health. Each item is rated on a five-point scale with a score of 1 reflecting a poor QoL and a score of 5 a very good QoL. Women were also asked about their desire for future fertility.

Study data was analysed using SPSS version 24.0 (SPSS Inc., Chicago, IL, USA). The descriptive analyses included frequencies, percentages for categorical data, ranges, means and standard deviations (SD) for continuous data. Linear regression analysis was used to assess which near miss conditions (hypertension, haemorrhage, medical disorders in pregnancy, non-pregnancy related infection or pregnancy-related infection) were independent predictors of score. The reliability of the WHOQOL-Bref was assessed using Cronbach's alpha with scores of 0.70 and over deemed acceptable.[11] A p-value of < 0.05 was considered significant. Ethical approval for the study was obtained from the University of Pretoria Research Ethics Committee (No. 125/2013).

6.3 RESULTS

There were 6536 deliveries at SBAH during the recruitment phase of the study (1 April 2013 – 30 March 2015). There were 133 near-misses and 10 maternal deaths during this period. The obstetric causes for the classification of a maternal near-miss are described in Table 1. One hundred and ten maternal near-misses and 55 control patients were recruited to the study. Fifteen maternal near-misses and 4 control subjects were lost to follow-up; 95 maternal near-misses and 51 control women completed the WHOQOL-Bref questionnaire. One woman in the control group had an uncomplicated low-risk ante-natal course but presented at term with loss of fetal movements and an intra-uterine fetal demise. A macerated term stillborn baby was delivered vaginally. The characteristics of the study population are shown in Table 2.

6.3.1 Table 1. Primary obstetric cause for a maternal near miss

Obstetric cause	**Number (%)**
Medical disease	23 (17.3)
Non-pregnancy related infection	4 (3.0)
Miscarriage	12 (9.0)
Pregnancy-related infection	3 (2.3)
Obstetric haemorrhage	49 (36.8)
Hypertension	39 (29.3)
Anaesthetic complications	2 (1.5)
Acute collapse – cause unknown	1 (0.8)

6.3.2 Table 2 Demographic data of the study population

Characteristics	Near-miss group (n=95)	Control group (n=51)	p-value
Age, years			
Mean (SD)	28,3 (6.83)	27,4 (7.14)	0.66
Range	18-46	20-42	
Race			
African, n (%)	85(89.5)	42(82.4)	
Caucasian, n (%)	5 (5.3)	4 (7.8)	
Coloured, n (%)	4 (4.2)	5 (9.8)	
Indian, n (%)	1 (1.0)	0 (0)	
Obstetric History			
Parity mean (range)	1.3 (0-4)	1.6 (0-5)	0.71
Timing of delivery			
< 34 weeks, n (%)	44 (46.3)	0 (0)	
34-37 weeks, n (%)	25 (26.3)	5 (9.8)	
>37 weeks, n (%)	26 (27.4)	46 (90.1)	
Live baby rate			
Number (%)	61 (64.2)	50 (98.0)	< 0.001
Tubal ligation or hysterectomy during pregnancy			
Yes, n (%)	11 (11.6)	2 (3.9)	
No, n (%)	84 (88.4)	49 (96.1)	

Table 3 represents mean score, standard deviation, and the percentage of respondents scoring at the highest (ceiling) and lowest (floor) level on the WHOQOL-Bref questionnaire. The control group scored significantly higher ($p<0.001$) for all questions on the WHOQOL-Bref except for bodily image ($p= 0.52$) where the difference in scores was not statistically significant. The highest scores for the near miss group and control groups were for pain (4.27) (daily life not affected by pain) and dependence on medical aids (4.94)

(medical treatment not needed to function normally) respectively. The lowest scores for both groups were lack of financial security (2.62 for near misses and 3.31 for the control group) suggesting that both groups did not have sufficient money for daily needs but this was a significantly greater problem for the near-miss group. The questions from the WHOQOL-Bref questionnaire were further grouped together into 4 domains evaluating physical and mental well-being, psychological health, social relations and the environment (Table 4). Near-miss women scored significantly lower for each domain compared to women in the control group. The Cronbach's alpha coefficient of the WHOQOL-Bref was adequate (0.964).

6.3.3 Table 3. Responses for each item on WHOQOL-Bref questionnaire

Items	Near Miss (n=95)			Control (n=51)			p-value
	Mean (SD)	*Floor n (%)*	*Ceiling n (%)*	*Mean (SD)*	*Floor n (%)*	*Ceiling n (%)*	
Overall QOL	3.56 (0.9)	2 (2.1)	13(13.7)	4.47 (0.6)	2 (3.9)	25 (49.0)	
Overall health	3.67 (1.0)	1 (1.1)	19 (20.0)	4.65 (0.5)	17 (33.3)	30 (58.8)	
Pain preventing daily work (5= not at all; 1= an extreme amount)	4.27 (0.9)	4 (4.2)	50 (52.6)	4.91 (0.3)	4 (7.8)	45 (88.2)	
Dependence of medical aids for daily function (5=not at all; 1= an extreme amount)	4.00 (0.9)	1 (1.1)	29 (30.5)	4.94 (0.2)	2 (3.9)	48 (94.1)	<0.001
Positive feeling	3.52 (0.9)	3 (3.2)	9 (9.5)	4.25 (0.7)	6 (11.8)	19 (37.3)	
Personal belief	3.46 (0.8)	1 (1.1)	5 (5.3)	4.20 (0.7)	10 (19.6)	20 (39.2)	
Concentration	3.74 (0.7)	2 (2.1)	7 (7.4)	4.61 (0.5)	1 (2.0)	31(60.8)	
Security	3.55 (0.9)	1 (1.1)	9 (9.5)	3.96 (0.8)	18 (35.3)	17(33.3)	
Physical environment	3.43 (0.9)	1 (1.1)	7 (7.4)	4.08 (0.8)	15(29.4)	19 (37.3)	
Energy	3.80 (0.8)	1 (1.1)	17 (17.9)	4.33 (0.5)	1 (2.0)	17 (33.3)	
Bodily image	3.71 (0.8)	6 (6.3)	14 (14.7)	3.80 (0.7)	18 (35.3)	8 (15.7)	0.52
Financial security	2.62 (0.9)	7 (7.4)	3 (3.2)	3.31 (0.7)	3 (5.9)	1 (2.0)	
Accessibility of information	2.98 (0.9)	29 (30.5)	5 (5.3)	4.02 (0.6)	1 (2.0)	8 (15.7)	
Leisure activity	2.87 (0.9)	5 (5.3)	4 (4.2)	4.16 (0.6)	1 (2.0)	14 (27.5)	
Mobility	3.18 (1.0)	1 (1.1)	8 (8.4)	4.12 (0.6)	6 (11.8)	12 (23.6)	
Sleep and rest	3.80 (0.9)	11 (11.6)	20 (21.1)	4.63 (0.5)	1 (2.0)	31 (60.8)	
Activities of daily living	3.87 (0.8)	5 (5.3)	16 (16.8)	4.69 (0.5)	16 (31.4)	34 (66.7)	
Work capacity	3.88 (0.8)	7 (7.4)	17 (17.9)	4.67 (0.6)	3 (5.9)	36 (70.6)	
Self-esteem	3.80 (0.8)	7 (7.4)	16 (16.8)	4.56 (0.5)	22 (43.1)	28 (54.9)	< 0.001
Personal relationship	3.71 (0.9)	1 (1.1)	18 (18.9)	4.27 (0.7)	6 (11.8)	19 (37.3)	
Sexual activity	3.78 (0.9)	2 (2.1)	21 (22.1)	4.08 (0.7)	12 (23.6)	15 (29.4)	
Social support	3.49 (0.9)	1 (1.1)	9 (9.5)	4.31 (0.6)	5 (9.8)	18 (35.3)	
Home environment	3.52 (0.9)	1 (1.1)	13 (13.7)	4.14 (0.7)	9 (17.7)	16 (31.4)	
Health care	3.74 (0.9)	10 (10.5)	17 (17.9)	4.45 (0.6)	4 (7.8)	25 (49.0)	
Transport	3.26 (0.9)	20 (21.1)	9 (9.5)	4.21 (0.6)	5 (9.8)	15 (29.4)	
Negative feeling	3.73 (0.9)	9 (9.5)	16 (16.8)	4.51 (0.6)	1 (2.0)	28 (54.9)	

6.3.4 Table 4. Comparison of Domain Scores for the near-miss and control groups

Domain	Domain score Near Miss Mean (SD)	Domain score Control group Mean (SD)	p-value
I Physical health and well-being	26.8 (4.2)	32.3 (2.3)	< 0.001
II Psychological health and well-being	21.9 (3.6)	26.0 (2.7)	< 0.001
III Social relations	11.0 (2.3)	12.7 (1.9)	< 0.001
IV Environment	26.0 (5.4)	32.5 (3.9)	< 0.001

Significantly more women in the control group compared with the near-miss group of women had a desire for more children (82.4% vs 43.2%; p < 0.001) (Figure 1). Almost 12% of women in the control group and 7.4% of near-miss women were uncertain about their desire for future fertility. Near-miss women scored the lowest when questioned about financial support. This was highlighted further in women's narratives where there were many references to loss of income either because of separation from a partner or loss of employment.

"The pregnancy caused a set-back in my life. I was forced to leave my job. Now I have money problems. My mother has to look after my 5-year old."

"I lost my job while in the hospital. I cannot get another job because I am too weak. I am getting a grant."

"My boyfriend broke-up with me because I lost the baby."

"I have marriage problems and I am very stressed."

Some women commented that attending the near-miss clinic allowed them to make new friends and they were able to develop a support system. QoL was compared for certain variables within the near miss group. Near miss women dependent on a social grant scored significantly lower for the following questions than near miss women not dependent on social support: pain ($p = 0.02$), dependence of medical aids ($p = 0.02$), bodily image ($p = 0.014$), mobility ($p = 0.025$) and negative feeling ($p = 0.033$). However there was no significant difference in any of the domain scores for near-miss women dependent on a social grant compared to those who were not. There were also no significant differences for all components of the QoL questionnaire or domain scores between near miss women who were HIV infected compared to those near miss women who were HIV negative.

Near-miss women who were discharged home with a perinatal loss scored significantly lower for the following components than near-miss women whose pregnancy resulted in a live baby: overall health ($p = 0.004$), positive feeling ($p = 0,002$), personal belief ($p = 0.001$), concentration ($p = 0.027$), security ($p = 0.031$), energy ($p = 0.004$), leisure activity ($p = 0.013$), self-esteem ($p = 0.029$) and home environment ($p = 0.033$). Near-miss women discharged home with a perinatal loss also scored significantly lower on 3 of the 4 domains: physical and mental well-being ($p = 0.009$), psychological health ($p = 0.007$) and the environment ($p = 0.03$). There was no significant difference between the 2 groups for the social relations domain, $p = 0.119$. A further sub-analysis was performed to compare the QoL of all women (near-miss and control group) who were discharged home with a live baby. Near-miss women whose pregnancy ended with a live baby scored significantly lower ($p < 0.001$) for all components on the QoL questionnaire and all domain scores except for: security ($p = 0.084$), bodily image ($p = 0.977$) and sexual activity ($p = 0.159$) than the control group.

The obstetric cause for a maternal near-miss among the 95 women who were recruited was: hypertension (n=37), obstetric haemorrhage (n=34), medical disease in pregnancy (n=20), non-pregnancy related infection (n=2) and pregnancy-related infection (n=2). We looked at the effect of the various near-miss conditions to determine if there was any effect on QoL. Maternal near-misses with a medical disease in pregnancy scored lower than the other groups for energy ($p = 0.022$; 95% CI -1.02 - -0.082), bodily image ($p = 0.02$; 95% CI -0.958 - -0.082), mobility ($p = 0.023$; 95% CI -1.140 - -0.086), physical health and well-being (Domain I) ($p = 0.017$; 95% CI -4.375 - -0.436) and psychological health and well-being (Domain II) ($p = 0.014$; 95% CI -3.849 - -0.436). There were no significant difference in QoL for women classified as a near-miss due to hypertension, haemorrhage, non- pregnancy related infection or pregnancy related infection.

6.4 DISCUSSION

This study provides important information in understanding how maternal complications affect the quality of life of women after pregnancy. One-year after a pregnancy complicated by an acute morbidity event, near-miss mothers scored significantly lower ($p < 0.001$) on all domains of the WHOQOL-Bref questionnaire which evaluated physical health and well-being (Domain 1), psychological health (Domain 2), social relations (Domain 3) and the environment (Domain 4). Some near-miss women suffer the double burden of acute morbidity during the peri-partum period and the additional misfortune of leaving the hospital without a living child. Only 64% of near-miss mothers left the hospital with a live child compared with 98% ($p < 0.001$) of women who experienced uncomplicated pregnancies. Near-miss mothers were also more likely to deliver a pre-term infant. Near-miss women who suffered a perinatal loss scored significantly lower on 9 components and 3 of the 4 domain scores of the QoL questionnaire than near miss women who were discharged home with a live child.[12] Fottrell et al, in a quantitative analysis of postpartum psychological

function, found that perinatal loss was important in initiating symptoms of psychological distress.[12] The authors found that at 12 months the overall effect of near-miss with perinatal death on risk of psychological distress was almost entirely mediated through financial debt, physical illness and marital disputes, each of which was exacerbated by the delivery complication and perinatal death. Unfortunately these adverse pregnancy events results in mother's carrying the long-term burden of an overall quality of life that is poorer than that of women who have had uncomplicated pregnancies and these symptoms are often carried with them in subsequent pregnancies.[13]

Near-miss women had the lowest scores for financial security. Factors that contributed to these problems were loss of income because women were unable to continue in jobs that they previously occupied or because the near-miss event resulted in separation from their partners. In some cases this lead to the break-down of the family unit when older children had to be cared for by other family members who did not live in the same house-hold. As a result of job-loss, some near-miss women became dependent on social support grants. Near-miss women receiving social grants had significantly lower scores for pain (women had more pain preventing daily work), dependence on medical aids (more dependent on medical support), bodily image, mobility and negative feelings than near miss women not dependent on social grants. Similar findings were reported by Filippi and Uzma who found that economic and social deprivation resulted in poor post-partum maternal health because women could not afford to seek healthcare when they needed it.[9,14] The terms "diversity" and "divergence" have been described in the recently published Lancet series on Maternal Health.[15] Diversity refers to the levels and causes of maternal health problems. Diversity, in turn, contributes to the divergence in the magnitude of maternal mortality, seen predominantly in vulnerable populations like sub-Saharan Africa. "Diversity" and "divergence" are therefore, the terms used to define the characteristics of poor maternal health in the 21st century.[15] Therefore some women are vulnerable by virtue of where they live and who they are. These women carry the risk of increased maternal morbidity which escalates further to a poor quality of life aggravated by a poor

social and economic burden. The women who had a maternal near-miss fall into this category.

There was almost double the difference in percentages of the ceiling effect for good personal relationships between the near-miss and control groups (18.9% vs 37.3% respectively). This means that double the proportion of women in the control group scored the maximum, reflecting possible strained personal relationships in the near miss group of women. A study of male partners' perceptions of a maternal near-miss event found that traumatic childbirth events provoke intense anxiety and fear in male partners which result in long-term consequences for them and their families.[16] Other studies have found that men experience alienation, disempowerment, information deprivation and exclusion from partners after an obstetric emergency.[17,18,19,20] Some men also become withdrawn from their social networks and are often reluctant to seek support as seeking help is in contradiction to societal expectations.[16] Anthropological studies in Africa have shown that the ability to bear children is not only a deeply personal experience that most women actively seek but is also a family and social obligation, the primary and sometimes only way women can acquire social status and recognition in their communities and is an essential event in continuity of marriage.[21,22]

The near-miss and control groups had similar ages and parities but there was a significant difference in the desire for future fertility. Although 88% of near miss women had surgical fertility preserved after the near-miss event, less than half (43.2%) had a desire for future fertility compared to 82.4% of controls. In a study by Camargo et al 72.8% of women who had an episode of maternal morbidity maintained their reproductive capacity, however only 7.5% of these women became pregnant again within the 5-year study period.[23] Furthermore women with a history of severe morbidity experienced a greater occurrence of complications and need for procedures in the subsequent pregnancies.[23] A study by Murphy and Charlett found that of the 50 women who required

intensive care during their index pregnancy, only 32 women conserved their potential fertility.[24] Of the 32 women 16 reported a subsequent pregnancy with a live birth, suggesting a fair reproductive outcome following an adverse event. However the high loss of reproductive potential probably reflects the severity of the adverse event and subsequent physical and emotional consequences.[23]

Several studies have reported that HIV infected mothers experience more morbidity and mortality in the first 2-years after delivery than HIV-uninfected women.[25,26,27] Our study has found no significant difference in QoL one-year after delivery between HIV-infected and HIV-uninfected women classified as a near-miss. We also did not find any significant differences in QoL when comparing the near miss conditions of hypertension, haemorrhage and pregnancy- and non-pregnancy related infection. Women with an underlying medical disorder, however, scored lower for energy, appearance and mobility scores. These women also scored lower on the domain scores for physical health and well-being and psychological health and well-being. Although all women classified as a near miss have a poorer QoL than women with uncomplicated pregnancies, women with medical disorders suffer additional physical and psychological distress.

This is the first study in South Africa comparing the QOL of near-miss women to that of women who experienced a low-risk pregnancy. However the study is limited in that only a portion of near miss patients were interviewed. Furthermore all women classified as a maternal near-miss had access to healthcare in the form of the maternal near miss clinic which they could attend if needed. Women attending these clinics were able to develop a support system with other mothers who had similar experiences. Therefore the present results cannot be generalised to the South African population as this is the only known near-miss clinic in the country. It is possible that women who do not have access to such a clinic may score lower on QOL questionnaires.

6.5 CONCLUSION

Women who experience a severe morbidity event during pregnancy have a poorer overall quality of life than women who experience uncomplicated pregnancies. A near miss event that is further complicated by a perinatal death contributes to even poorer long-term physical, psychological and environmental well-being. Further research needs to be done to determine which support services should be established to assist women after traumatic experiences of pregnancy.

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CONCLUSION AND RECOMMENDATIONS

INTRODUCTION

This thesis was developed to test the hypothesis:

Women who suffer a severe acute morbidity event during pregnancy suffer from long-term physical and mental impairment.

Below are the key findings of this thesis.

Determining the potential size of the problem and immediate ways to prevent severe acute maternal morbidity:

Chapter 1: Maternal near miss and maternal death in the Pretoria Academic Complex

Approximately 5% of women in the Pretoria Academic complex develop a potentially life-threatening condition as defined by the WHO and 25% of these women develop a life-threatening condition.[1,2] This means that 120 women suffer severe acute morbidity in the Pretoria Academic Complex annually and survive.[1] The five potentially life-threatening conditions identified by the WHO are: severe postpartum haemorrhage, severe pre-eclampsia, eclampsia, sepsis/severe infection and ruptured uterus.[3] Other important causes of severe obstetric morbidity identified in the Pretoria Academic Complex are: antepartum haemorrhage, non-pregnancy related infections and medical and surgical conditions in pregnancy.[1] The objective of identifying a woman as potentially high risk is to ensure that strategies are implemented to prevent the occurrence of an acute emergency event. Such strategies include prevention or early identification of a disease that may potentially cause harm. Fifteen percent of cases of severe pre-eclampsia, 13% of cases of obstetric haemorrhage and 7% of cases of organ dysfunction due to medical disease in pregnancy are not predicted antenatally and these women need emergency care and transfer to a tertiary institution.[1]

Chapter 2: Barriers to obstetric care among maternal near misses

Eighty-three percent of near miss women encounter some form of barrier before they reach the appropriate level of care required to manage their condition.[4] Lack of knowledge of the problem by patients (40%), inadequate ante-natal care (37%), delay in patient admission, referral and treatment (37%) and substandard care (36%) are important barriers to care that near-miss women face. Almost 40% of these women book at a level 1 or 2 facility for ante-natal care with no identifiable risk factors and later develop an acute condition requiring transfer to a tertiary facility. Certain acute conditions such as post-partum haemorrhage and severe pre-eclampsia cannot be predicted ante-natally and health care workers at all levels need to be equipped to stabilise and treat the emergency condition until the ill mother reaches the appropriate level of care. In pre-eclampsia the average time between the last ante-natal visit and a near-miss event is 2.6 weeks. The WHO protocol for ante-natal visits for low-risk pregnant women recommends a visit to the ante-natal clinic every 6 weeks.[5] This time period is too infrequent to detect changes and requires revision to timeously detect cases of pre-eclampsia.

Long-term effects of severe pre-eclampsia

There are approximately 26 600 deliveries in the PAC annually and more than 680 women develop pre-eclampsia. Chapters 3,4 and 5 have highlighted some of the long-term complications of severe pre-eclampsia. The findings emphasises the need to prevent the development of pre-eclampsia, particularly severe pre-eclampsia and for early diagnosis and referral of patients.

Chapter 3: Cerebral white matter lesions after pre-eclampsia

Almost half of the pre-eclamptic women in this study developed cerebral WMLs 1-year after delivery.[6] Expectant management of severe pre-eclampsia especially for those women requiring 2 or more drugs to control blood pressure in pregnancy is associated with an increased risk of developing cerebral white matter lesions (WMLs) 1-year after delivery. The use of 2 or more drugs for hypertension control should be considered a threshold at which women should be counselled about

future health and possible termination of pregnancy. White matter lesions are an important indicator of future risk of disease and are associated with an increased risk of stroke, dementia and death.[7]

The incidence of chronic hypertension 1 year after delivery in our study population, who had a mean age of 28 years, was 61%. This increased rate was most likely because 95% of the study population was of African origin. Compared to other racial groups, African women are at greater risk of developing pre-eclampsia with severe complications.[8] In the general population hypertension increases the risk for the development of WMLs.[9] This may explain the increased prevalence of WMLs (65% versus 32%) in women with chronic hypertension compared to those women who were normotensive at 1 year.

Chapter 4: Cardiac diastolic function after recovery from pre-eclampsia

This study describes the cardiac function of women who developed severe pre-eclampsia during pregnancy. Women with early onset pre-eclampsia requiring delivery prior to 34 weeks are at an increased risk of cardiac diastolic dysfunction at one-year post-partum and this is irrespective of the presence of chronic hypertension.[10] Diastolic dysfunction precedes the onset of systolic dysfunction in 50% of cardiac diseases and systolic dysfunction further precedes the onset of heart failure.[11] The hazard ratio for all-cause mortality for mild diastolic dysfunction is 8.31.[12]

The difference in cardiac diastolic dysfunction at 1-year in women with early and late-onset pre-eclampsia can be explained by proposed differences in pathophysiology. The placentas of women with early onset disease differ significantly from those who develop pre-eclampsia at term. The former group demonstrate placental findings consistent with insufficiency and vascular lesions while late-onset disease is characterised by placental hyperplasia and unimpaired

fetal growth.[13,14,15,16] Early onset of pre-eclampsia is therefore a risk for poor long-term maternal health and physicians must weigh the risks and benefits of early versus expectant management of pregnancy in this group of women.

Chapter 5: The effect of pre-eclampsia on retinal microvascular caliber at delivery and post-partum

The pre-eclamptic disease process results in maternal vascular dysfunction with increased peripheral resistance. In chapter 5 we demonstrated that endothelial dysfunction and vessel narrowing which are clinical manifestations of pre-eclampsia, persist after delivery. We confirmed that retinal arteriolar narrowing in women with pre-eclampsia persists for up to 1-year post-partum. The changes in retinal microvasculature in women with pre-eclampsia reflect permanent, long-term microvascular dysfunction and are related to both subclinical and clinical end-organ damage. Retinal arteriolar narrowing has also been found to be a risk factor for future hypertension, coronary heart disease and stroke.[17, 18, 19, 20]

Consequences of severe morbidity in pregnancy

Chapter 6: Quality of life one year after severe acute maternal morbidity

Chapter 6 provides important information in understanding how maternal complications affect quality of life (QoL) of women after pregnancy. A severe acute morbidity event in pregnancy reduces the desire for future reproduction and results in a poorer QoL when compared to women with uncomplicated pregnancies. One-year after a pregnancy complicated by an acute morbidity event, near-miss mothers scored significantly lower on all domains of the WHOQOL-Bref questionnaire which evaluated physical health and well-being (Domain 1), psychological health (Domain 2), social relations (Domain 3), and the environment (Domain 4). Furthermore, some near-miss women suffer the double burden of acute morbidity and a perinatal loss. Unfortunately, a maternal near-miss event that is complicated by a perinatal loss results in an overall QoL that is poorer than a near-miss event where a mother is discharged home with a live baby.

SUMMARY

For every woman who dies in pregnancy in the Pretoria Academic Complex, 6 others will suffer severe morbidity.[1] Approximately 416 women will develop chronic hypertension, 327 will develop cerebral white matter lesions and 75 women will develop cardiac diastolic dysfunction 1-year after experiencing a pregnancy complicated by pre-eclampsia. Over one year 120 women from the Pretoria Academic Complex will require some specialised follow-up to improve their health and quality of life.

There has been considerable effort in the last decade in South Africa and other middle-income countries to improve maternal mortality rates using targets such as the Millennium and Sustainable Development goals. Although these are important goals this study has shown that women who survive pregnancy complications are an equally important group who require both medical and psychosocial postpartum care. A significant proportion of morbidity events occurring during pregnancy are believed to be preventable, however the consequences constitute a public health cost with elevated financial and social costs.[21] Hypertensive disease is a growing public health problem in Africa.[8] The most recent Confidential Enquiry into Maternal Mortality in South Africa for 2014-2016 has reported reductions in maternal mortality due to conditions such as non-pregnancy related infections and obstetric haemorrhage.(Saving Mothers Report, unpublished) However maternal deaths in South Africa due to hypertension are on the rise. Traditionally optimal management of severe pre-eclampsia depends on balancing the risks to the mother and fetus from pregnancy prolongation versus the risk of prematurity to the neonate from immediate delivery.[22] This study has highlighted important long-term consequences for women who develop severe pre-eclampsia but survive pregnancy. The MEXPRE Latin study found no neonatal benefit with expectant management of pre-eclampsia from 28-34 weeks.[23] Early delivery of women with severe pre-eclampsia may prevent long-term maternal complications but this would have to be confirmed in a randomised control trial comparing expectant versus aggressive management of pre-eclampsia.

RECOMMENDATIONS

1. Women who experience a severe acute morbidity event in pregnancy must be recognised as a vulnerable group who require increased postpartum care and surveillance. Ideally all regional and tertiary centres should have near-miss clinics for post-partum care. Any risk factors for future disease should be identified and modified to promote long-term health.

2. Women who have survived a near-miss event should receive post-partum psycho-social counselling. They should also be counselled about future pregnancy risk. Additional resources, facilities and health –worker training would be required to provide specialised care to approximately 120 women annually in the Pretoria Academic Complex. Nationally there are approximately 1.2 million births per year in South Africa; this translates to 15 000 women who should have intensive post-natal follow-up for at least one year. This is a public health challenge.

3. Women who develop severe pre-eclampsia in pregnancy should be monitored for the development of chronic hypertension. Additional resources, clinic facilities and staff are required to accommodate 680 women who develop pre-eclampsia in the PAC every year. Nationally this would mean that approximately 31 200 women would require monitoring for the development and treatment of chronic hypertension.

4. The following is a proposed protocol for the post-partum follow-up of women who experience severe acute morbidity and/or pre-eclampsia in pregnancy:
   - All pregnant women should follow-up at their local clinic/hospital for the routine post-natal visit as recommended currently by the National Department of Health of South Africa.

   - Women who developed pre-eclampsia during pregnancy or those who were classified as a maternal near miss should be seen at a dedicated near-miss clinic at the closest regional or tertiary hospital after 6 weeks post-partum

- The following tests/examinations should be performed at the 6-week post-natal visit: vital signs, urine dipstix, a complete physical examination and a short 5- question screening test for post-partum depression. The following is an example of a post-natal screening tool:

  Over the past month, have you often felt:

  1. *Nervous, anxious or panicky*
  2. *Unable to stop worrying or thinking too much?*
  3. *Down, depressed or hopeless?*
  4. *Little interest or pleasure in doing things that you used to enjoy?*
  5. *You had plans and plans to harm yourself?*

- The patient should receive psychosocial counselling regarding the morbidity event in pregnancy and further support if there was any perinatal loss/morbidity.

- In addition women with pre-eclampsia should have a basic echocardiogram and should be should be referred to specialist physicans/cardiologists if they have developed chronic hypertension or if any abnormality is detected on echocardiography.

- Women who have tested positive on the post-partum depression screening test should be referred to psychiatric/social services units

- Women with no abnormalities detected at the 6-week post-natal visit should be seen again at 6 months and 1 –year at dedicated near miss clinics where further psycho-social assessment/counselling should be performed. Pre-eclamptic women should have their blood pressure checked at the 6 month visit and blood pressure and echocardiography assessments should be repeated at 1-year.

5. Health care workers at all levels of care should be able to recognise, stabilise and transfer patients with acute obstetric emergencies. The healthcare chain from the time of presentation to the transfer of an acutely ill patient to the appropriate level of care must be maintained. This would necessitate that ambulance staff be trained to administer acute emergency drugs needed for obstetric care.

6. Fire-drills in obstetric emergencies should be practised by labour ward teams. This would improve the care of women who are initially classified to be having a low risk pregnancy but who present later in the pregnancy with an acute condition requiring emergency management.

7. Patients should be educated about the importance of ante-natal care and the symptoms and warning signs of the major obstetric conditions.

8. Since the publication of chapter 2, the South African Department of Health has increased the number of ante-natal visits for low risk women. Healthcare workers should have a high index of suspicion for pre-eclampsia in women with new onset hypertension and/or proteinuria.

9. Pre-eclampsia is associated with long-term cardiovascular risk. All pregnant women with risk factors for the disease should be offered prophylaxis with aspirin and calcium before 16 weeks gestation.

10. Further research needs to be conducted to determine:
    a. The relation between cerebral white matter lesions and neurocognitive function

    b. Whether early delivery of women with pre-eclampsia would be protective against future cardiovascular and cerebrovascular risk.

    c. Whether echocardiography is indicated routinely in post-partum pre-eclamptic women as a screening tool for future cardiovascular disease. The

value of a limited echocardiography performed by obstetricians/maternal medicine specialists should be explored.

d. Why 6% of women develop cardiac diastolic dysfunction at 1 year after an uncomplicated low-risk pregnancy.

e. Whether new biochemical diagnostic aids such as the sFLT/PLGF ratio should be considered in women with suspected pre-eclampsia so that the disease process can be identified in the early stages.

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ADDENDUM

List of publications and request for permissions

LIST OF PUBLICATIONS

1. Soma-Pillay P, Pattinson RC, Langa-Mlambo L, Nkosi BSS, Macdonald AP. Maternal near miss and maternal death in the Pretoria Academic Complex, South Africa: A population-based study. SAMJ 2015; 105(7): 578-583.

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Maternal near miss and maternal death in the Pretoria Academic Complex, South Africa: A population-based study

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Background. In order to reduce maternal mortality in South Africa (SA), it is important to understand the process of obstetric care, identify weaknesses within the system, and implement interventions for improving care.
Objective. To determine the spectrum of maternal morbidity and mortality in the Pretoria Academic Complex (PAC), SA.
Methods. A descriptive population-based study that included all women delivering in the PAC. The World Health Organization definition, criteria and indicators of near miss and maternal death were used to identify women with severe complications in pregnancy.
Results. Between 1 August 2013 and 31 July 2014, there were 26 614 deliveries in the PAC. The institutional maternal mortality ratio was 71.4/100 000 live births. The HIV infection rate was 19.9%, and 2.7% of women had unknown HIV status. Of the women, 1 120 (4.2%) developed potentially life-threatening conditions and 136 (0.5%) life-threatening conditions. The mortality index was 14.0% overall, 30.0% for non-pregnancy-related infections, 2.0% for obstetric haemorrhage and 13.6% for hypertension. Of the women with life-threatening conditions, 39.3% were referred from the primary level of care. Vascular, uterine and coagulation dysfunctions were the most frequent organ dysfunctions in women with life-threatening conditions. The perinatal mortality rate was 26.9/1 000 births overall, 23.1/1 000 for women with non-life-threatening conditions, and 198.0/1 000 for women with life-threatening conditions.
Conclusion. About one in 20 pregnant women in the PAC had a potentially life-threatening condition; 39.3% of women presented to a primary level facility as an acute emergency and had to be transferred for tertiary care. All healthcare professionals involved in maternity care must have knowledge and skills that equip them to manage obstetric emergencies. Review of the basic antenatal care protocol may be necessary.

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There were 4 452 maternal deaths in South Africa (SA) for the period 2011 - 2013.[1] The institutional maternal mortality ratio (iMMR) in SA decreased from 176.22/100 000 live births in the 2008 - 2010 triennium to 154.06/100 000 for 2011 - 2013, but further work needs to be done to meet the fifth Millennium Development Goal. In order to reduce maternal mortality, it is important to understand the process of obstetric care, identify weaknesses within the system, and finally implement interventions for improving care.[2]

A woman who experiences and survives a severe health condition during pregnancy, during childbirth or after delivery is classified as a maternal near miss.[3] By studying cases of maternal deaths and near misses, important information can be obtained about the processes that take place in healthcare systems responsible for the care of pregnant women. While near-miss cases share many pathological and circumstantial characteristics with maternal deaths, they provide additional information about obstacles that have to be overcome after the onset of an acute complication.[2,4] Although a maternal near-miss case can only be identified retrospectively, it is clinically useful to prospectively identify women with potentially life-threatening conditions. A woman who develops a life-threatening condition will either become a maternal near-miss case or a maternal death.

Objectives

To determine the spectrum of severe maternal morbidity and mortality in the Pretoria Academic Complex (PAC), SA, and compare the data with previous surveys and the World Health Organization (WHO) Multicountry Survey on Maternal and Newborn Health.[5] The WHO study was used as a comparison because it is the only study to characterise maternal morbidity occurring in a worldwide network of health facilities.

Methods

This was a descriptive population-based study that took place from 1 August 2013 to 31 July 2014 at nine delivery facilities in central, south-western and eastern Tshwane, Gauteng Province, SA. The following delivery units were included in the study: Steve Biko Academic Hospital (SBAH) (level 3), Kalafong Provincial Tertiary Hospital Hospital (KAH) (level 3), Mamelodi Hospital (level 2), Tshwane District Hospital (TDH) (level 1), Pretoria West Hospital (level 1), Laudium Community Health Centre (CHC) with midwife obstetric unit (MOU), Eersterust MOU, and Stanza Bopape and Dark City clinics (CHCs). SBAH and KAH are tertiary referral hospitals that receive referrals from outside Gauteng, but data were only analysed for women living in the Tshwane region; those living outside were excluded. Cases of abortion and ectopic pregnancy were also

excluded from the study. Delivery data were recorded on a daily basis at all the health facilities, and daily audit meetings were held at SBAH and KAH to identify women with life-threatening conditions and organ dysfunction in pregnancy. The following WHO indicators were used to quantify women with severe complications in pregnancy:[2,6]

Maternal near miss. A woman who nearly died but survived a complication that occurred during pregnancy or childbirth, or within 42 days of termination of pregnancy. The WHO near-miss criteria are listed in Table 1.

Maternal death. A maternal death is the death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and the site of pregnancy, from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes.

Life-threatening conditions/severe maternal outcome (SMO). This refers to all women who either qualified as having a maternal near miss or who died. It is the sum of maternal near misses and maternal deaths.

Potentially life-threatening condition. The five potentially life-threatening conditions described by the WHO are severe postpartum haemorrhage, severe pre-eclampsia, eclampsia, sepsis/severe systemic infection, and ruptured uterus. The operational definitions of the five potentially life-threatening conditions are:

- *Severe postpartum haemorrhage.* Genital bleeding after delivery, with at least one of the following: perceived abnormal bleeding (1 000 mL or more) or any bleeding with hypotension or blood transfusion.
- *Severe pre-eclampsia.* Persistent systolic blood pressure of ≥160 mmHg or a diastolic blood pressure of ≥110 mmHg; proteinuria of ≥5 g in 24 hours; oliguria of <400 mL in 24 hours; and HELLP (haemolysis, elevated liver enzymes, low platelets) syndrome or pulmonary oedema. Excludes eclampsia.
- *Eclampsia.* Generalised fits in a patient without previous history of epilepsy. Includes coma in pre-eclampsia.
- *Severe sepsis/systemic infection.* Presence of fever (body temperature >38ºC), a confirmed or suspected infection (e.g. chorioamnionitis, septic abortion, endometritis, pneumonia), and at least one of the following: heart rate >90 bpm, respiratory rate >20/min, leucopenia (white blood cells <4 × 10^9/L), leucocytosis (white blood cells >12 × 10^9/L).
- *Uterine rupture.* Rupture of uterus during labour confirmed by laparotomy.

Severe maternal outcome ratio (SMOR). This refers to the number of women with life-threatening conditions per 1 000 live births. This indicator gives an estimation of the amount of care that would be needed in an area.

Mortality index (MI). The number of maternal deaths divided by the number of women with life-threatening conditions, expressed as a percentage.

Descriptive statistics in the form of means and standard deviations in the case of continuous data and frequencies and percentages in the case of categorical data were calculated. Ethical approval was obtained from the University of Pretoria Ethics Committee (No. 125/2013).

Results

There were 26 614 deliveries in the PAC (SBAH, KAH, Mamelodi Hospital, TDH, Pretoria West Hospital, Laudium CHC with MOU, Eersterust MOU, Stanza Bopape MOU and Dark City clinics) during the study period. One hundred and thirty-six women developed life-threatening conditions, and there were 19 maternal deaths. The SMOR was 5.1/1 000 births and the MI 14.0%. The caesarean section rate was 25.2% overall and 61.0% for women with life-threatening conditions. The HIV infection rate was 19.9% for the general population, 23.1% for near misses and 36.8% for mothers who died. HIV status was unknown in 2.7% of patients. The spectrum of morbidity from uncomplicated pregnancies to maternal death is illustrated in Fig. 1.

Table 1. The WHO near-miss criteria[6]

Clinical criteria
Acute cyanosis
Oliguria unresponsive to fluids or diuretics
Jaundice concomitantly with pre-eclampsia
Shock
Cerebrovascular accident
Breathing rate >40 - <6/min
Loss of consciousness, no pulse/heartbeat
Gasping
Coagulation disorders
Total paralysis
Laboratory criteria
Oxygen saturation <90% for >60 minutes
Creatinine >300 µmol/L or >3.5 mg/dL
Unconscious, presence of glucose and ketoacidosis in urine
PaO_2/FiO_2 <200 mmHg
Acute thrombocytopenia (platelets <50 × 10^9/L)
Bilirubin >100 µmol/L or >6.0 mg/dL
Lactate >5 mg/dL
pH <0.1
Management criteria
Use of continuous vasoactive drug
Puerperal hysterectomy due to infection or haemorrhage
Transfusion >5 units of red cell concentrate
Dialysis for treatment of acute kidney failure
Cardiopulmonary resuscitation
Intubation and ventilation for >60 minutes, unrelated to anaesthesia

PaO_2/FiO_2 = ratio of partial pressure of arterial oxygen and fraction of inspired oxygen.

Most of the patients with potentially life-threatening and life-threatening conditions were treated at the two PAC tertiary level hospitals. Forty-six women (39.3%) who were classified as near misses and 7 (36.8%) who died had to be transferred to the tertiary level hospitals after initially presenting at a lower level of care. The most frequent indications for emergency transfer of women with life-threatening conditions to the tertiary hospitals were severe pre-eclampsia (15.4%, *n*=21), obstetric haemorrhage (13.2%, *n*=18) and organ dysfunction in women with underlying medical disease (6.6%, *n*=9) (Table 2). The MI was 18.6% for SBAH, 10.2% for KAH and 12.5% for Mamelodi Hospital.

Twenty-six women (22.2%) who were classified as a near miss had not booked with antenatal care services or had had infrequent visits. Medical practitioners caring for these patients believed that lack of antenatal care may have contributed to the life-threatening event. The distribution of patients with potentially life-threatening

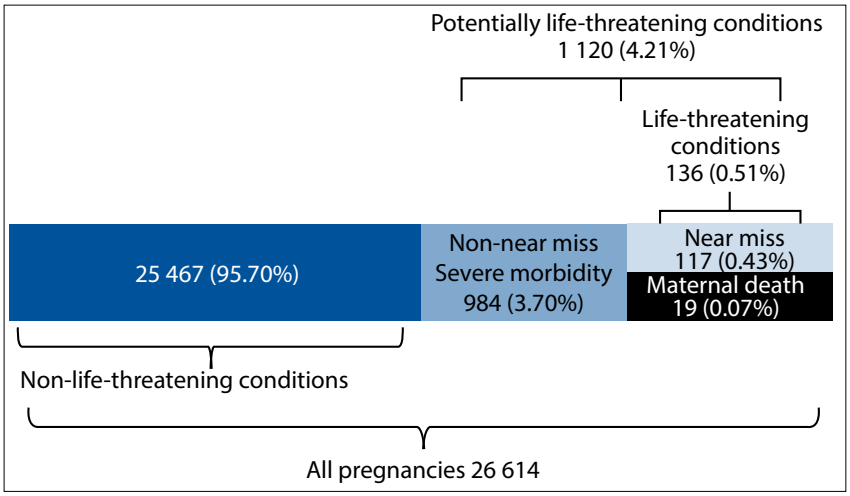

Fig.1. The spectrum of morbidity from uncomplicated pregnancies to maternal death (not drawn to scale).

Table 2. Acute life-threatening conditions necessitating tertiary care (*N*=136)

Condition	Patients referred to tertiary centre from lower levels of care *n* (%)	Patients already in tertiary care *n* (%)
Obstetric haemorrhage	18 (13.2)	26 (19.1)
Pre-eclampsia	21 (15.4)	22 (16.2)
Sepsis	3 (2.2)	11 (8.1)
Medical/surgical disorders	9 (6.6)	9 (6.6)
Non-pregnancy-related infections	3 (2.2)	8 (5.9)
Anaesthetic disorders	-	4 (2.9)
Other	-	2 (1.5)
Total	54 (39.7)	82 (60.3)

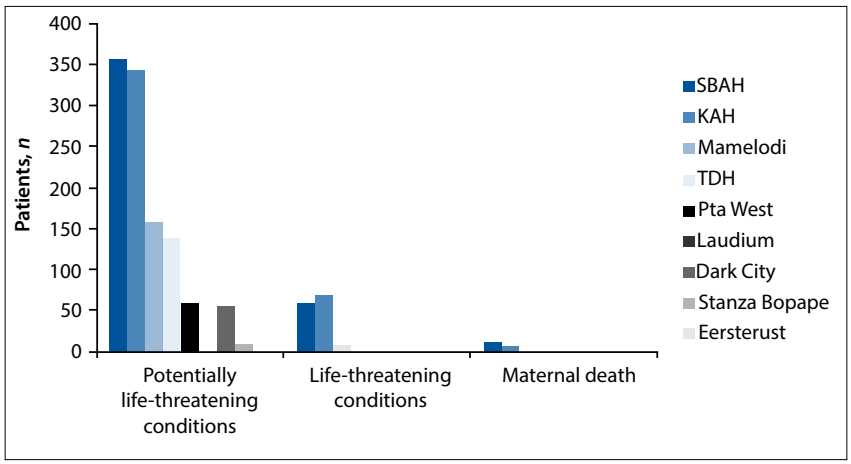

Fig. 2. Distribution of potentially life-threatening conditions, near misses and maternal deaths in relation to the different levels of care.

conditions in relation to the different levels of care is shown in Fig. 2.

The frequency of potentially life-threatening disorders is shown in Table 3. (Antepartum haemorrhage and non-pregnancy-related infections that are not part of the WHO definition of potentially life-threatening conditions have been included.)

The MI for non-pregnancy-related infections was 30.0%, for obstetric haemorrhage 2.0%, for hypertension 13.6% and for medical and surgical disorders 19.0% (Table 4).

The near-miss markers and distribution of organ dysfunction are shown in Tables 5 and 6. The average age of the women who were classified as a near miss was 30.3 years (minimum 16, maximum 43); 34 (29.1%) were primigravidas and 83 (70.9%) were multigravidas. There were 6 maternal deaths related to HIV and AIDS; 4 patients had respiratory failure secondary to TB pneumonia, 1 had bacterial meningitis and 1 died after presenting with multiorgan failure and milliary tuberculosis. Six women died of complications related to pre-eclampsia: 1 patient had a liver rupture, 2 had intracranial bleeds, 2 had respiratory failure due to pulmonary oedema and 1 had a cardiac arrest. The patient who died as a result of postpartum haemorrhage had a placenta praevia and had had two previous caesarean sections. Although an antenatal ultrasound scan had confirmed the location of the placenta, the diagnosis of placenta accreta was missed. Surgeons encountered a major bleed at caesarean section, and despite two re-look laparotomies the bleeding could not be controlled. Four patients died due to underlying medical disease, 1 each due to breast cancer, acute-on-chronic pancreatitis and an anaesthetic complication in a diabetic patient, while the 4th patient had a prosthetic heart valve.

There were no maternal deaths at the level 1 hospitals or CHCs and only one death at a level 2 hospital. This was a patient with advanced-stage breast cancer who was unable to obtain transport to a tertiary-level facility. The MIs for the two tertiary hospitals were 18.6% (SBAH) and 10.15% (KAH), and that for the level 2 hospital was 12.5%.

Table 7 compares the indices of severe acute maternal morbidity at the PAC for the periods 1997 - 1998, 2002 - 2004 and 2013 - 2014. Although the SMOR for the general population has remained the same since 1997 - 1998, both the iMMR and the MI have decreased. These findings are consistent for postpartum haemorrhage and hypertension. The SMOR for puerperal sepsis has remained constant despite the HIV epidemic with a decrease in MI. The SMOR and MI for medical and surgical conditions remain unchanged.

Fig. 3 illustrates the perinatal mortality related to maternal morbidity. The women with severe maternal morbidity and mortality had a much high perinatal mortality rate (PNMR); however, for every woman with a complicated pregnancy, almost five women had no life-threatening condition. This explains the relatively small difference between the total PNMR and the PNMR of the non-life-threatening conditions.

The primary obstetric causes of perinatal death were unexplained intrauterine death (30.3%), spontaneous preterm labour (25.5%), antepartum haemorrhage

(12.3%), intrapartum asphyxia (9.3%), hypertensive disorders (7.4%), fetal abnormality (6.9%) and maternal disease (3.7%).

Discussion

To our knowledge, this is the first study in SA assessing the spectrum of morbidity for a specific region. There were 26 614 deliveries over a 12-month period (2013 - 2014). This represents almost a doubling of deliveries since 1997 - 1998, when the total number of births for the biennium was 27 025, and a 35% increase since 2002 - 2004 (51 469 births).[7] Just over 4% of women developed a potentially life-threatening condition and 0.5% developed a life-threatening condition. This is lower than the WHO Multicountry Survey on Maternal and Newborn Health, which reported an incidence of 7% for potentially life-threatening conditions and 1% for life-threatening conditions.[5] However, the difference between the two studies was that ours was population based while the WHO study was hospital based.

About 40% of women with acute life-threatening conditions did not present directly to the two tertiary level hospitals during the acute stage of disease. These patients were booked at a level 1 or 2 facility and then developed an acute condition requiring urgent transfer. Similarly, the England Collaborative Group reported that a significant proportion of serious complications occur in women with no recognisable risk factors.[8] Severe pre-eclampsia, obstetric haemorrhage and organ dysfunction due to an underlying medical condition were the most important reasons for emergency transfer. This indicates the need to have all healthcare professionals involved in care of pregnant women trained in the initial stabilisation and management of obstetric and neonatal emergencies. The antenatal care protocol used in our complex is based on the WHO recommendation of four antenatal visits for low-risk patients.[9] The low frequency of visits possibly means

Table 3. Frequency of potentially life-threatening disorders

	All women (*N*=26 614) *n* (%)	Women with SMO (*N*=136) *n* (%)	HIV infection in women with SMO *n* (%)
Severe haemorrhage	660 (2.5)	51 (37.5)	7 (13.7)
Antepartum haemorrhage	301 (1.1)	17 (12.5)	1 (5.9)
Postpartum haemorrhage	336 (1.3)	31 (22.7)	4 (12.9)
Ruptured uterus	23 (0.1)	3 (2.2)	2 (66.7)
Severe hypertensive disorders	682 (2.6)	44 (32.4)	4 (9.1)
Pre-eclampsia	457 (1.7)	40 (29.4)	4 (10.0)
Eclampsia	225 (0.8)	4 (2.9)	-
Other complications			
Puerperal sepsis	35 (0.1)	14 (10.3)	2 (14.3)
Non-pregnancy-related infections		20 (14.7)	20 (100.0)

Table 4. MIs for different disease conditions

Underlying condition	Maternal near miss, *n*	Maternal death, *n*	MI, %
Obstetric haemorrhage	50	1	2.0
Antepartum haemorrhage	17	0	0
Ruptured uterus	3	0	0
Postpartum haemorrhage	30	1	3.2
Hypertension	38	6	13.6
Chronic	1	0	0
Pre-eclampsia	35	4	10.0
Eclampsia	2	2	50.0
Puerperal sepsis	14	0	0
Non-pregnancy-related infections	14	6	30.0
Medical/surgical disorders	17	4	19.0

Table 5. Markers for classification of a maternal near miss (*N*=117)

Near-miss marker	*n* (%)
Cerebrovascular accident	2 (1.7)
Total paralysis	1 (0.9)
Oxygen saturation <90% for >60 minutes	6 (5.1)
Acute thrombocytopenia (platelets <50 × 10^9/L)	26 (2.2)
Creatinine >300 µmol/L or > 3.5 mg/dL	4 (3.4)
Bilirubin >100 µmol/L or > 6.0 mg/dL	1 (0.9)
Ketoacids in urine	4 (3.4)
Use of continuous vasoactive drug	3 (2.6)
Dialysis for acute renal failure	2 (1.7)
Hysterectomy following infection or haemorrhage	35 (29.9) (infection 14, haemorrhage 21)
Cardiopulmonary resuscitation	3 (2.6)
Transfusion of >5 units red cells	31 (26.5)
Intubation and ventilation for >60 minutes	18 (15.4)

Table 6. Organ system dysfunction in women with life-threatening conditions (*N*=136)*

Dysfunction	*n* (%)
Vascular dysfunction (hypovolaemia)	54 (39.7)
Uterine dysfunction	35 (25.7)
Coagulation dysfunction	27 (19.9)
Respiratory dysfunction	24 (17.7)
Cardiovascular dysfunction	9 (6.6)
Immunological dysfunction	8 (5.9)
Renal dysfunction	8 (5.9)
Cerebral dysfunction	7 (5.2)
Hepatic dysfunction	5 (3.7)
Metabolic dysfunction	5 (3.7)

*Some women had more than one organ dysfunction.

Table 7. Comparison of the indices of severe acute morbidity rates at the PAC for the periods 1997 - 1998, 2002 - 2004 and 2013 - 2014

	1997 - 1998			2002 - 2004			2013 - 2014		
	SMOR	iMMR	MI	SMOR	iMMR	MI	SMOR	iMMR	MI
Antepartum haemorrhage	1.0	0	0	0.9	1.9	2.1	0.6	0	0
Postpartum haemorrhage	1.4	7.4	5.3	2.1	15.5	7.5	1.2	3.8	3.2
Hypertension	1.5	33.3	22.5	1.57	19.4	12.3	1.6	22.5	13.6
Puerperal sepsis	0.4	7.4	20.0	0.5	5.8	10.7	0.5	0	0
Non-pregnancy-related infections	0.3	22.2	66.7	0.4	19.4	47.6	0.8	22.5	30.0
Medical and surgical disorders	0.8	11.1	14.3	0.8	11.7	14.3	0.8	15.0	19.0
Total (excluding early pregnancy losses)	5.8	96.2	16.6	7.0	85.5	12.2	5.1	71.4	14.0

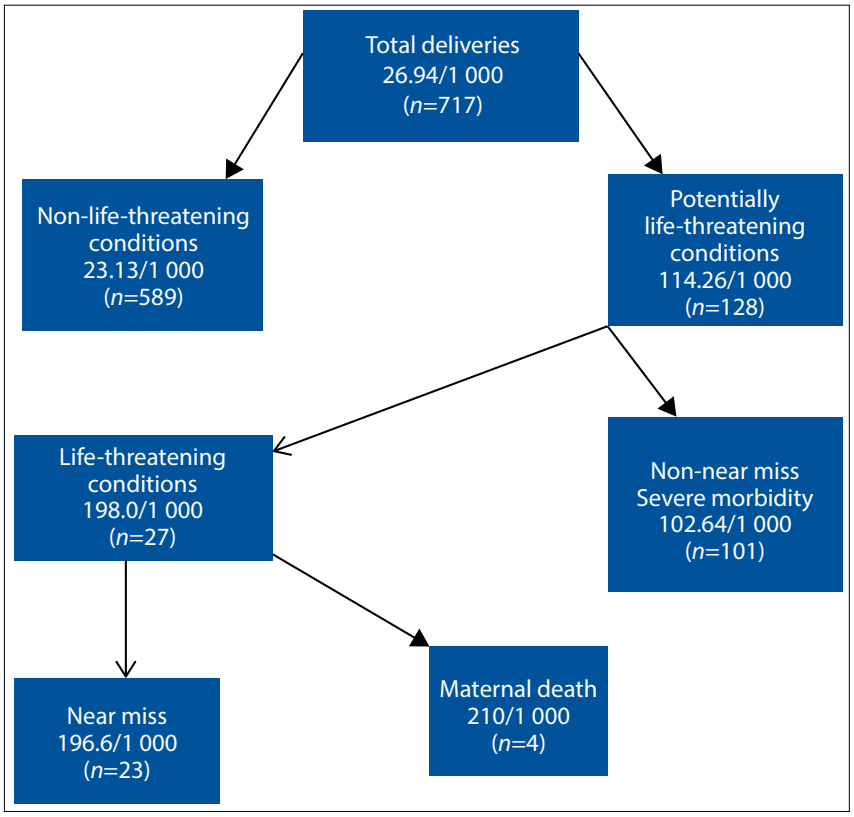

Fig. 3. Perinatal mortality rate (for babies >500 g).

that cases of pre-eclampsia in the early stages of the disease process were missed, leading to patients presenting at a later stage with acute complications requiring tertiary care. Early detection of pre-eclampsia may require revision of our current antenatal care protocol and is supported by the recent Cochrane review on patterns of routine antenatal care for low-risk pregnancy.[10]

There has been a decrease in the iMMR and MI at the PAC since 1997. This has been associated with decreases in MI for postpartum haemorrhage, hypertension, puerperal sepsis and non-pregnancy-related infections. The MI for non-pregnancy-related infections in the PAC was 66.7% in 1997 - 1999, 75% in 2000, 47.6% in 2002 - 2004 and 30% in 2013 - 2014.[8,11] The decrease reflects the implementation of the antiretroviral programme by the National Department of Health and better handling of respiratory complications. Of significance is the low MI for postpartum haemorrhage (3.2%), which is less than half of the rate (7.5%) reported in 2002 - 2004 and significantly lower than the rate (5.3%) reported for 1997 - 1998.[11,12] The decrease in MI for severe postpartum haemorrhage and puerperal sepsis is probably a result of the introduction of strict protocols. The frequency of postpartum haemorrhage in women with life-threatening conditions (22.7%) was similar to that in the WHO study (26.7%).[6] However, the rates of pre-eclampsia (29.4%) and non-pregnancy-related infections (14.7%) were greater in our study (WHO 16.3% and 1.6%, respectively). The rate of pre-eclampsia in women with life-threatening conditions was consistent with reports from Nigeria (32.5%) and Mozambique (32.9%).[13,14]

Vascular (hypovolaemia), uterine (hysterectomy) and coagulation (low platelets) dysfunction were the most frequent organ system dysfunctions in women with life-threatening conditions (Table 6). Many women had multiple complications. The disease profile in our complex has changed since the year 2000, when vascular, cardiac, immunological and coagulation dysfunction were the most important organ systems causing obstetric morbidity.[15] Obstetric haemorrhage was the potentially life-threatening condition most frequently encountered in our complex (37.5%), and vascular dysfunction as a result of hypovolaemia was the most common organ system dysfunction seen. The low MI for postpartum haemorrhage suggests that although postpartum haemorrhage is an important problem, the condition is well managed by our clinicians.

Of the five potentially life-threatening conditions, hypertensive disorders contributed to 7.4% of perinatal deaths. Ninety-three per cent of perinatal deaths were not related to antepartum and intrapartum maternal life-threatening conditions, and if postpartum maternal life-threatening conditions are included, 80% of the women with perinatal deaths did not have severe morbidity. These findings are consistent with those of Allanson *et al.*[16] describing perinatal mortality in Mpumalanga Province, SA, and Vogel *et al.*[17] in the WHO Multicountry Survey, who found that a significant proportion of women have no recognisable obstetric or medical condition at the time of perinatal death. Allanson *et al.*[16] found a rate of maternal complications in macerated stillbirths, fresh stillbirths and early neonatal deaths of 50.4%,

50.7% and 25.8%, respectively. The WHO Multicountry Survey found a maternal complication rate of 22.9%, 27.7% and 21.2% in late macerated stillbirths, late fresh stillbirths and early neonatal deaths, respectively. Current early antenatal identification of both severe maternal morbidity and perinatal mortality is inadequate.

Study strengths and limitations

The strength of this study is the robust method of data collection. The new national birth register records maternal complications, facilitating the collection of data. The PAC has been collecting and reviewing data on life-threatening conditions for more than 15 years, and all doctors are familiar with the WHO near-miss criteria. Women who were classified as a near miss were interviewed about barriers encountered in accessing healthcare. This information will be presented in a separate article.

A limitation of this study is the exclusion of cases of early pregnancy loss (abortions and ectopic pregnancies). Some cases of sepsis may have been missed if patients presented late in the postpartum period. Furthermore, maternal infections such as pneumonia, tuberculosis and meningitis were not on the list of potentially life-threatening conditions, so the SMOR could not be calculated for these disease conditions. The list of potentially life-threatening conditions should be expanded to include medical conditions and non-pregnancy-related infections. This is supported by Lumbiganon *et al.*,[18] who demonstrated that indirect causes of maternal deaths are increasingly important in developing countries, with indirect causes being responsible for about one-fifth of severe maternal outcomes.

Recommendations

- The WHO has identified five potentially life-threatening conditions: severe postpartum haemorrhage, severe pre-eclampsia, eclampsia, sepsis/severe infection and ruptured uterus.[2] Our study has shown that conditions such as abruptio placentae, non-pregnancy-related infections and medical and surgical disorders are also important causes of obstetric morbidity, and the WHO should therefore consider expanding its categories of potentially life-threatening conditions.
- Forty per cent of patients with life-threatening conditions presented to a level 1 or 2 facility before being transferred for tertiary care. Cases of postpartum haemorrhage and severe pre-eclampsia could not be predicted antenatally. In addition, no recognisable obstetric condition was present in the majority of pregnancies that ended in a perinatal death. Health workers in level 1 and 2 centres must therefore be able to recognise, stabilise and transfer pregnant women and neonates presenting with an acute obstetric emergency.
- Strategies to prevent and screen for pre-eclampsia and improvement of emergency transport for women are essential in order to reduce obstetric morbidity and mortality.
- Review of the reduced visits protocol put forward by the WHO should be considered, as increasing the frequency of antenatal visits for low-risk women may increase detection of pre-eclampsia at an earlier stage of the disease process.[8] However, this would require a considerable increase in resources.

Conclusion

In this study we were able to identify the proportion of pregnancy-related morbidity in our population and compare it with other studies. The MI and prevalence of potentially life-threatening conditions were similar to those in the WHO Multicountry Survey. Although there has been a decrease in the MI for non-pregnancy-related infection, further interventions need to be implemented to reduce morbidity and mortality associated with HIV disease and tuberculosis. A significant proportion of women who developed severe maternal conditions were not identified during the antenatal period, indicating the need to ensure that all levels of care can manage the initial steps in obstetric and neonatal emergencies and that an efficient emergency transport system is available.

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Barriers to obstetric care among maternal near-misses

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Background. There are several factors in the healthcare system that may influence a woman's ability to access appropriate obstetric care.
Objective. To determine the delays/barriers in providing obstetric care to women who classified as a maternal near-miss.
Methods. This was a descriptive observational study at Steve Biko Academic Hospital, a tertiary referral hospital in Pretoria, South Africa. One hundred maternal near-misses were prospectively identified using the World Health Organization criteria. The 'three-delays model' was used to identify the phases of delay in the health system and recorded by the doctor caring for the patient.
Results. One or more factors causing a delay in accessing care were identified in 83% of near-miss cases. Phase I and III delays were the most important causes of barriers. Lack of knowledge of the problem (40%) and inadequate antenatal care (37%) were important first-phase delays. Delay in patient admission, referral and treatment (37%) and substandard care (36%) were problems encountered within the health system. The above causes were also the most important factors causing delays for the leading causes of maternal near-misses – obstetric haemorrhage, hypertension/pre-eclampsia, and medical and surgical conditions.
Conclusions. Maternal morbidity and mortality rates may be reduced by educating the community about symptoms and complications related to pregnancy. Training healthcare workers to identify and manage obstetric emergencies is also important. The frequency of antenatal visits should be revised, with additional visits in the third trimester allowing more opportunities for blood pressure to be checked and for identifying hypertension.

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Obstetric emergencies may occur in women with known risk factors (pre-existing medical disease or recurrent miscarriage) or may be caused by pregnancy itself, gestational hypertension or obstetric haemorrhage. A significant proportion of serious complications in pregnancy occur in women with no recognisable risk factors.[1,2] A serious complication may progress rapidly to a life-threatening situation. Access and timely referral to appropriate emergency obstetric care are therefore important components of the healthcare system. The World Health Organization (WHO) estimates that about 88 - 98% of maternal deaths can be avoided with timely access to existing emergency obstetric intervention.[3] However, there is increasing evidence that the majority of women classified as near-miss cases in developing countries arrive at referring hospitals in a critical condition.[4]

Several factors may influence a woman's ability to access appropriate obstetric care. Thaddeus and Maine[5] developed the 'three-delays' model in 1994. The model evaluates circumstances surrounding access to appropriate emergency obstetric care. The three components are as follows: phase I delay – delay in deciding to seek care by the individual and/or family; phase II delay – delay in reaching an adequate healthcare facility; and phase III delay – delay in receiving adequate care at the healthcare facility. Several authors have used the three-delays model to investigate delays related to maternal morbidity and mortality.

A maternal near-miss is defined as a woman who nearly died as a result of but survived a complication that occurred during pregnancy or childbirth.[6] Studying circumstances around near-miss cases has an advantage over cases of maternal death because near-miss patients are able to provide direct information after an event.

Objective

To determine the reasons for delay in accessing appropriate obstetric care for women who were classified as maternal near-misses.

Methods

This was a descriptive observational study performed at Steve Biko Academic Hospital (SBAH), Pretoria, South Africa (SA), from 1 August 2013 to 30 October 2015. SBAH is a tertiary referral hospital that serves as a referral hospital for the central and eastern Tshwane regions. Patient referrals are mainly from a level 1 hospital (Tshwane District Hospital) situated adjacent to SBAH and a level 2 hospital (Mamelodi Hospital) in Tshwane east. Very ill patients may be referred directly from midwife obstetric units in the referral area. Obstetric patients with underlying medical disease may be referred in from neighbouring provinces.

One hundred near-miss cases were prospectively identified at daily audit meetings at SBAH using the WHO criteria for a maternal

Table 1. The three-delays model

A. Community-level factors associated with delay in seeking healthcare (phase I)
Desire for home delivery
Lack of knowledge of the problem
Inadequate antenatal care (late attendance/delayed visits)
Non-compliance with healthcare provider's advice
Belief in alternative care
Family member prevented woman from accessing healthcare
B. Factors associated with delay in reaching the health system (phase II)
Lack of finance
Lack of transport
C. Factors associated with delays in the health system (phase III)
Delay in patient admission, referral or treatment
Lack of resources (blood/intensive care)
Substandard care (inappropriate diagnosis or treatment)

near-miss.[7] Data were recorded by the doctor caring for the patient. Information on antenatal care was obtained from case notes recorded on the patient's antenatal card, from the maternity case record and from patient interviews. The antenatal care schedule for low-risk patients adopted by our district is based on the WHO model of reduced visits: booking and 20, 26, 32 and 38 weeks, with an appointment at the hospital at 41 weeks. The three-delays model[5] was used to evaluate reasons for delay. Table 1 describes the factors in each phase that were evaluated in the study. Phase III delays include all delays within the healthcare system, from the moment a patient presents to a health facility, irrespective of the level of care, until she receives the appropriate care for her condition.

Statistical analysis

Descriptive statistics in the form of means and standard deviations (SDs) in the case of continuous data and frequencies and percentages in the case of categorical data were calculated. Ethical approval was obtained from the University of Pretoria Ethics Committee (ref. no. 125/2013).

Table 2. Antenatal history and monitoring (*N*=100 near-miss cases)

Age (yr), mean (SD) (range)	29.7 (6.3) (17 - 46)
Parity, mean (range)	1.4 (0 - 4)
Medical history, *n*	
Chronic hypertension	6
Diabetes mellitus	7
Cardiac disease	10
Other	12
Timing of event, *n*	
Antenatal	62
Intrapartum	7
Postpartum	31
Presence of obstetric complications during pregnancy, *n*	
Yes	23
No	67
Unknown/unbooked	10

Results

Data were collected for 100 maternal near-miss cases. Forty-one patients were referred in from other institutions, while 59 were known to the hospital or presented directly with an acute obstetric emergency. Information on antenatal history and monitoring is shown in Table 2.

The most important obstetric causes for a maternal near-miss were obstetric haemorrhage (*n*=31), medical and surgical disorders (*n*=31), and complications of hypertension and pre-eclampsia in pregnancy (*n*=24). One or more factors causing a delay in accessing care were identified in 83% of near-miss cases (Table 3). Phase I and III delays, in particular lack of knowledge of the problem (40%),

Table 3. Barriers to accessing care for maternal near-misses (*N*=100)

	n
Community-level factors associated with delay in seeking healthcare (phase I)	
Desire for home delivery	0
Lack of knowledge of the problem	40
Inadequate antenatal care (late attendance/delayed visits)	37
Non-compliance with healthcare provider's advice	16
Belief in alternative care	6
Family member prevented woman from accessing healthcare	2
Factors associated with delay in reaching the health system (phase II)	
Lack of finance	6
Lack of transport	8
Factors associated with delays in the health system (phase III)	
Delay in patient admission, referral or treatment	37
Lack of resources (blood/intensive care)	14
Substandard care (inappropriate diagnosis or treatment)	36

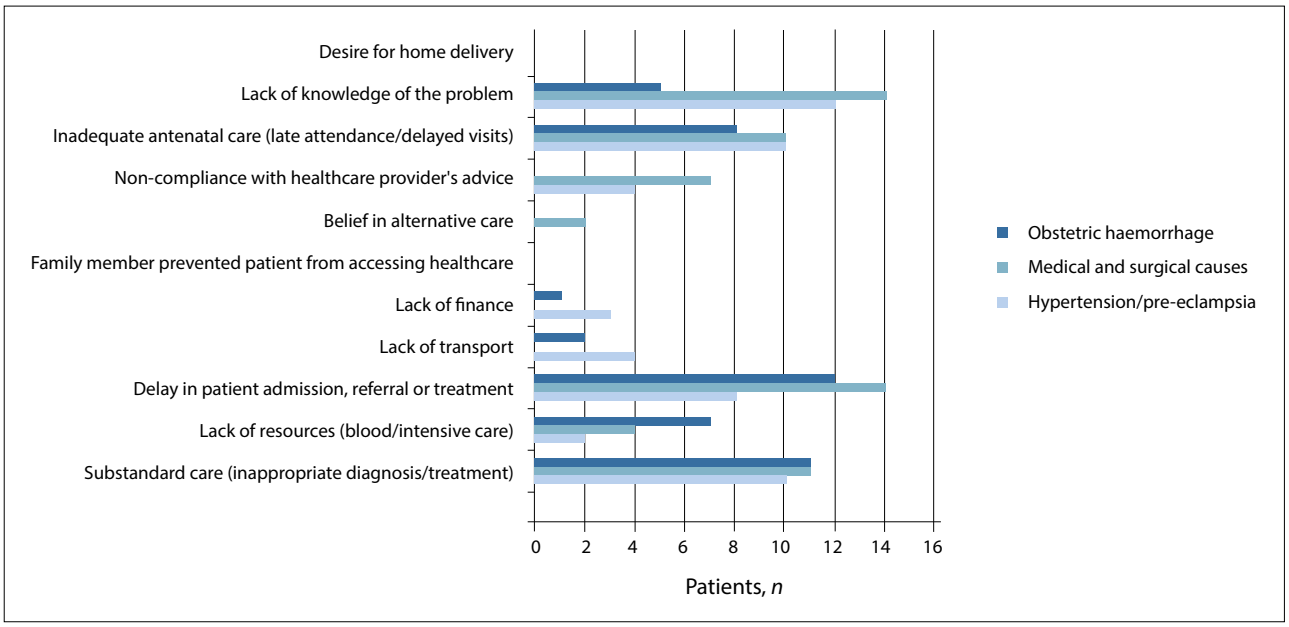

Fig. 1. Barriers to accessing care in cases of obstetric haemorrhage, medical and surgical disorders and hypertension and pre-eclampsia.

inadequate antenatal care (37%), delay in patient admission, referral and treatment (37%) and substandard care (36%), were the most common factors in the study population. These factors were also the most important contributors when cases of obstetric haemorrhage, medical and surgical disease and hypertension in pregnancy were analysed separately (Fig. 1).

The near-miss events among hypertensive patients occurred between 24 and 38 weeks' gestation, with most occurring between 26 and 38 weeks (Table 4 and Fig. 2). Five (21%) of the patients categorised as hypertensive near-misses were unbooked, while booking information was not available for four patients (17%). The average time between the last antenatal visit and the near-miss event was 2.6 weeks.

Table 4. Timing of events of hypertensive near-misses (*N*=24)

Patient no.	Gestational age at near-miss event (wk)	Gestational age at last antenatal clinic visit prior to near-miss event (wk)
1	31	29
2	32	28
3	24	Unbooked
4	26	26
5	36	36
6	37	32
7	30	26
8	35	Unbooked
9	38	37
10	28	28
11	32	26
12	29	29
13	37	Unknown
14	39	Unbooked
15	Postpartum	Normotensive at delivery
16	34	32
17	27	24
18	27	Unbooked
19	30	26
20	26	Unbooked
21	37	Unknown
22	37	32
23	30	Unknown
24	33	Unknown

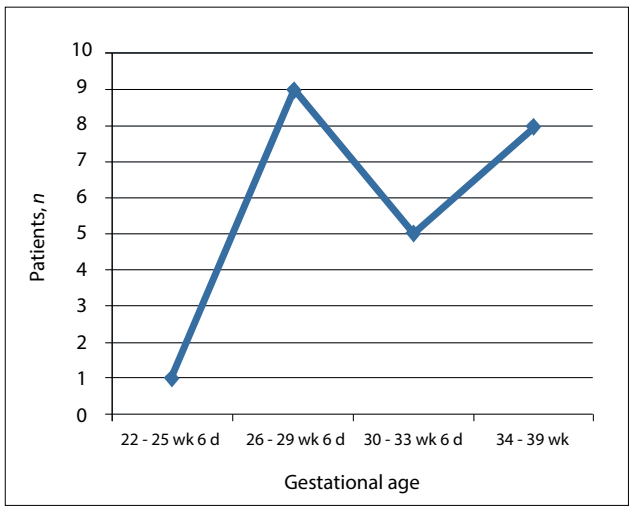

Fig. 2. Gestational age at which hypertensive near-miss events occurred.

Phase III delays were significant barriers encountered by patients with obstetric haemorrhage. Delay in recognising the problem of bleeding, delay in initiating steps to stop bleeding and delay in patient transfer were the problems identified in 75% of cases. Lack of intensive care beds and lack of blood and blood products were problems observed in 17% of cases. There were two cases of antepartum haemorrhage in patients with undiagnosed placenta praevia. Both patients were booked, but the location of the placenta was not recorded on the ultrasound report. There were three cases of uterine rupture. Two patients had had unsafe terminations of pregnancy requiring hysterectomy, and the other patient had had two previous caesarean sections, was unbooked and presented in labour with uterine rupture. Obstetric haemorrhage related to abruptio placentae was an important cause of morbidity. Inadequate antenatal care for abruptio placentae related to hypertension and delay in patient transfer were important avoidable factors.

There were six maternal near-misses due to parasuicide/unsafe termination of pregnancy. In these cases, lack of knowledge of the problem (4/6), inadequate antenatal care (5/6) and non-compliance with healthcare worker advice (3/6) were the most important barriers identified. These were also the most important factors in cases of non-pregnancy-related infections.

Discussion

This study shows an unacceptably high rate of barriers encountered by patients during pregnancy. Sixty-six percent of near-miss patients encountered more than one delay. Inadequate antenatal care and lack of patient knowledge of the underlying problem were important phase I delays. Inadequate antenatal care was a problem in 37% of cases. This is similar to the rate of 30% found in a Brazilian study in which an association between delay in seeking healthcare services and maternal near-miss and death was observed.[8] Delay in seeking health services was 2.5 times more frequent in maternal near-miss patients and increased six-fold in mothers who died compared with women who had uncomplicated pregnancies.[8] More than a quarter of our patients (29% of pre-eclamptic near-misses and 26% of near-misses with medical disease) had risk factors for hypertension in pregnancy, had an underlying medical condition but booked after 20 weeks' gestation, or had inadequate antenatal care due to non-compliance with the required antenatal visits. Several studies in low- and middle-income countries have shown that many women are unable to judge the severity of their disease pathology and may only seek care once their condition becomes life-threatening.[9-11] This highlights the need for community education about pregnancy risks, which may be promoted by encouraging all women to register with mobile phone/web-based sites such as MomConnect. After a complicated pregnancy, mothers should also be counselled about future pregnancy risks.

All the hypertensive near-miss events occurred between 24 and 39 weeks, with peaks between 26 and 39 weeks. Almost 60% of these patients booked for antenatal care, but their acute condition could not have been detected in time with the current protocol of antenatal visits. Similarly, the Birthplace in England Collaborative Group[2] reported that a significant proportion of serious complications occur in women with no recognisable risk factors. The antenatal care protocol used in our complex is based on the WHO recommendation of four antenatal visits for low-risk patients.[12] Unfortunately this protocol was unable to detect and prevent an acute hypertensive emergency timeously. The average time between the last antenatal

visit and the near-miss event was 2.6 weeks. The period between antenatal visits using our current guidelines is 6 weeks. This time period is too infrequent to detect significant changes in blood pressure. The current guideline on the frequency of antenatal visits should be revised as additional visits, especially in the third trimester, should be implemented. Blood pressure must be recorded at every visit. Alternatively, an integrated approach to antenatal care could be considered whereby a pregnant mother visits a day clinic, undertakes home monitoring or is examined by an occupational nurse at the workplace so that her blood pressure can be recorded every 2 weeks from 24 weeks' gestation.

Delay in patient admission, referral and treatment and substandard care were important barriers identified for near-miss cases related to haemorrhage, hypertension and medical disease in pregnancy. Obstetric haemorrhage is a medical emergency that requires timely diagnosis and aggressive resuscitation and management by the labour ward team. Fire-drills in obstetric emergencies should be practised by labour ward teams. The National Committee for Confidential Enquiries into Maternal Deaths in SA has proposed a referral algorithm for patients with underlying cardiac and medical disease in pregnancy.[13] All patients with underlying medical disease should be risk-assessed and referred timeously to the appropriate level of care. Such protocols should also be followed for other obstetric emergencies.

Study strengths and limitations

This is the first study in SA in which near-miss patients provided a direct account of obstacles they had to overcome before receiving the appropriate form of healthcare.

The study is limited because it involves only one tertiary institution, but we believe that the situation would be similar at other sites, as the delays detected are common in maternal deaths due to hypertension.[13]

We do not know how many patients with hypertension were detected and managed appropriately. However, the high institutional maternal mortality ratio (iMMR) of hypertension in pregnancy, and the fact that the iMMR has been relatively constant for a decade, suggest a health system problem in detecting and managing hypertension. The problem (of a protocol of reduced antenatal visits) has been demonstrated clearly in this study.

Conclusions

Obstetric morbidity may be reduced by overcoming barriers preventing patients from accessing care. Healthcare managers need to continually assess and revise policies to improve obstetric care. This study has shown that the current schedule of antenatal care visits should be revised so that women are seen more frequently during pregnancy and their blood pressure can be monitored. Patient education and healthcare worker training need to be strengthened.

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Cerebral white matter lesions after pre-eclampsia

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ABSTRACT

Background: Women who have had pre-eclampsia in their previous pregnancies demonstrate a greater prevalence of cerebral white matter lesions several years after the pregnancy than women who have been normotensive during their pregnancy. Both the pathophysiology and the timing of development of these lesions are uncertain. White matter lesions, in the general population, are associated with an increased risk of stroke, dementia and death.

Aims and objectives: The objective of the study was to determine the prevalence of cerebral white matter lesions amongst women with severe pre-eclampsia at delivery, 6 months and 1 year postpartum and to establish the possible pathophysiology and risks factors.

Methods: This was a longitudinal study performed at Steve Biko Academic Hospital, a tertiary referral hospital in Pretoria South Africa. Ninety-four women with severe pre-eclampsia were identified and recruited during the delivery admission. Magnetic resonance imaging (MRI) of the brain was performed post – delivery and at 6 months and 1 year postpartum.

Results: Cerebral white matter lesions were demonstrated in 61.7% of women at delivery, 56.4% at 6 months and 47.9% at 1 year. Majority of the lesions were found in the frontal lobes of the brain. The presence of lesions at 1 year post-delivery was associated with the number of drugs needed to control blood pressure during pregnancy (OR 5.1, 95% CI 2.3–11.3, $p < 0.001$). The prevalence of WMLs at 1 year was double in women with chronic hypertension at 1 year compared to those women who were normotensive (65.1% vs 32.3%).

Conclusion: Women who require 2 or more drugs to control blood pressure during pregnancy have an increased risk of developing cerebral white matter lesions after delivery.

1. Introduction

Pre-eclampsia is a pregnancy specific disorder characterised by new onset hypertension after 20 weeks gestation. The pathogenesis of pre-eclampsia is still poorly understood but it is widely established that the disease contributes to gross maternal vascular dysfunction [1]. Cerebrovascular abnormalities are an important complication and neurological symptoms are often reported. Cerebral complications are the single most common cause of hypertensive maternal deaths in South Africa [2].

Pregnancy is associated with significant changes in both the cardiovascular and cerebral circulations [3]. Physiological changes such as decreased vascular resistance, hyperpermeability and increased cardiac output are necessary to perfuse vital organs such as the placenta and uterus [3]. Hemodynamic changes in the brain such as increased permeability of cerebral vessels increase the potential for development of oedema, raised intracranial pressure and other neurological symptoms [4]. Additionally, a rapid rise in blood pressure during the pre-eclamptic process can result in disruption of the cerebral autoregulation mechanism and blood-brain barrier [5].

The posterior reverse encephalopathy syndrome (PRES) is a condition characterised clinically by headaches, altered mental status, seizures, blurred vision and distinct MR imaging appearance [6]. It is currently believed that the pathophysiological process of PRES is responsible for the cerebral oedema in pre-eclamptic women who present with neurological symptoms [6]. Magnetic resonance imaging usually reveals widespread hemispheric watershed vasogenic oedema concentrated mainly in the parietal and occipital lobes of the brain [7]. Both clinical symptoms and radio-

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logical findings resolve after elimination of etiological factors [8]. Brain lesions associated with PRES are thought to be the result of the disturbance of the cerebral autoregulation mechanism and impairment of endothelial function [9]. Cerebral autoregulation is the ability of the cerebral vasculature to maintain a stable cerebral blood flow within a certain range of blood pressure values [10]. This is facilitated by constriction in conditions of high blood pressure and dilatation when blood pressure is low [11]. Cerebral blood flow remains stable if the mean arterial blood pressure does not exceed 150 mmHg or falls below 50–60 mmHg [11]. Disruption of the autoregulation mechanism occurs with forced vasodilatation of the cerebral resistance vessels and subsequent hyperperfusion when blood pressure exceeds the upper limit of autoregulation. The cerebral autoregulation mechanism consists of myogenic and neurogenic components [9]. Endothelial damage deceases the functional effect of the myogenic mechanism [12]. In these conditions regulation of cerebral perfusion is taken over by neurogenic mechanisms. Areas of the brain that are poorly innervated by sympathetic nerves (posterior circulation areas) become sensitive to blood pressure elevation and extravasation of fluid occurs when elevation in blood pressure exceeds the autoregulation capacity of blood vessels in the brain [7]. Lesions associated with PRES are therefore often demonstrated in the posterior aspects of the brain. Anterior parts of the brain which have a greater sympathetic supply are protected from overperfusion by a vasoconstrictive effect [7]. Early diagnosis and treatment of clinical features associated with PRES may result in total resolution of both radiological and clinical features [13].

White matter lesions or "leukoaraiosis" refers to neuroimaging abnormalities of the cerebral white matter which are visible as bilateral and either patchy or diffuse areas of hypodensity on CT or hyperintensity on T2-weighted MRI [14]. Although the pathogenesis of cerebral white matter lesions is unknown, cerebral ischemia is believed to play an important role [14]. These lesions are frequently observed on neuroimaging modalities in the ageing population and persons who have a history of stroke [14]. Other risk factors include arterial hypertension, diabetes mellitus and cardiac disease [14]. In the general population, the prevalence of cerebral white matter lesions varies between 11 and 21% in adults aged 64 to 94% at the age of 82 [15]. How hypertension or ageing contribute to white matter lesions is uncertain but WMLs in both the elderly and hypertensive patients are possibly the result of damage to cerebral small vessels [16]. Raised blood pressure, and other vascular disorders cause alterations of the small arteries and arterioles of the cerebral white matter. Smooth muscle cells are replaced by fibo-hyaline material causing thickening of vascular walls and narrowing of their lumen [14]. It is believed that these alterations in cerebral vasculature cause a reduction in blood supply to white matter and this further leads to localised ischemic areas of necrosis or diffuse leukoaraiosis which is irreversible. Furthermore WML progression has been found to be less in controlled treated hypertensives compared with uncontrolled untreated hypertensives [17,18] White matter lesions due to cerebral small vessel disease are not related to WMLs due to PRES as the distribution of lesions is different and WMLs due to PRES are reversible.

Recently studies have demonstrated an increased prevalence of cerebral white matter lesions in formerly pre-eclamptic women [19,20]. Aukes et al. have reported a prevalence, at 5–6 years after delivery, of 41% in formerly eclamptic, 37% in formerly pre-eclamptic women compared with 17–21% in a control group of normotensive patients [19,20]. The aim of this study was to assess the presence and severity cerebral white matter lesions amongst pre-eclamptic patients at delivery, 6 months and 1 year postpartum and determine the possible pathophysiology and associated risk factors.

2. Methods

This was a longitudinal study of maternal near misses and women with potentially life-threatening complications at Steve Biko Academic Hospital from 1 April 2013 to 30 March 2016. Recruitment of pre-eclamptic patients for this phase of the study took place from 1 April 2013to 30 March 2015 and follow-up visits took place from 1 April 2014 to 30 March 2016. The Radiology Department at Steve Biko Academic Hospital reserved MRI-imaging appointments every Monday during the study period. Post-partum women (day 2–7) with severe pre-eclampsia were identified on a Monday morning and if fit to be transported to the MRI unit were informed of the study. MRI studies were performed on patients who consented to the procedure and were agreeable to follow-up studies. Follow-up scans were performed at 6 months and 1 year postpartum. When studying follow-up MRI scans, the radiologist was able to compare studies at delivery to determine whether lesions had enlarged or regressed. The radiologist also looked for new emerging lesions.

As per hospital protocol, all patients with severe pre-eclampsia were managed expectantly until 34 weeks if maternal and fetal condition was satisfactory. Magnesium sulphate was administered to pre-eclamptic women for the following indications:

- Treatment of eclamptic convulsions.
- Symptoms and signs of imminent eclampsia such as severe headaches, visual disturbances and/or epigastric pain.
- Prior to transport of patients with severe acute hypertension from referring centres.

The first-line therapy for the treatment of hypertensive disorders in pregnancy was oral methyl dopa. The second and third line agents to control blood pressure were an oral calcium channel blocker (nifedipine or amlodipine) and prasozin. Nifedipine short-acting (10 mg) or intravenous labetalol was used for the management of severe acute hypertension in pregnancy. The goal of treatment was to maintain a systolic blood pressure of 140–160 mmHg and a diastolic blood pressure of 90–110 mmHg. Hypertensive disorders were classified according to the classification and diagnosis of the International Society for the Study of Hypertension in Pregnancy (ISSHP) [21]. The following definitions were used:

Severe hypertension/uncontrolled – blood pressure >160/110 mmHg.
Low blood pressure – blood pressure <100/60 mmHg.
Rescue therapy – short acting anti-hypertensive treatment administered if blood pressure is >160/110 mmHg.
Episodes of severe hypertensive days – number of days during which a blood pressure of 160/110 mmHg or more was recorded.

The MRI studies were performed on a 1.5 Tesla Phillips Achieva System at the Radiology Department at Steve Biko Academic Hospital, Pretoria, South Africa. Five millimetre slices with a 20% gap and a matrix of 256 × 256 was used. The sequences used were: T1 sagittal (repetition time (TR) = 2.11 ms; echo time (TE) = 2.4 ms), FLAIR axial (TR = 11 000 ms; TE = 100 ms), T2 axial (TR = 6059 ms; TE = 100 ms), T2 coronal (TR = 3281 ms; TE = 100 ms), Magnetic Resonance Angiography (MRA) (TR = 25 ms; TE = 6.9) and Diffusion Weighted Imaging (DWI) (TR = 3518 ms; TE = 89 ms). The WMLs were measured according to largest diameter in categories of small (<3 mm), medium (3–10 mm) or large (greater than10 mm). The radiologist analysing

the MRI images was blinded to the clinical information of the study patients.

Descriptive statistics in the form of means and standard deviations in the case of continuous data and frequencies and percentages in the case of categorical data was calculated. Binary logistic regression was used to establish if any factors had an impact on outcome. A p-value of <0.05 was considered significant. Ethical approval was obtained from the University of Pretoria Ethics Committee (No. 125/2013).

3. Results

There were 6536 deliveries at our hospital during the recruitment phase of the study (1 April 2013–30 March 2015). Four-hundred and sixty-three (7.1%) women presented with severe pre-eclampsia and of these 106 women were recruited to the study. Seven women were lost to follow-up and five declined testing at different stages of the study. Data was therefore available for 94 women. Fourteen (14.9%) women were known with chronic hypertension and developed superimposed pre-eclampsia during pregnancy. Thirty-four (36.2%) women developed HELLP syndrome and twenty-three (24.5%) were eclamptic. The demographic information for the study population is shown in Table 1.

Cerebral white matter lesions (WMLs) were found in 58 (61.7%) women at delivery, 53 (56.4%) at 6 months and in 45 (47.9%) women at 1 year. Twenty-one women showed evidence of PRES on diffusion weighted images at delivery. Of these 21 women, 9 (42.9%) demonstrated WMLs at 1 year. Therefore majority of lesions (80%) visualised at the 1 year MRI study were in women without evidence of PRES at delivery.

Table 1
Demographic data of the study population (n = 94).

Race	
African, n (%)	89 (94.7%)
White, n (%)	2 (2.1%)
Coloured, (%)	2 (2.1%)
Indian, n (%)	1 (1.1%)
Age	
Mean (SD)	28.3 (6.8)
Range	18–46
Obstetric History	
Parity mean (range)	1.1 (0–4)
Medical conditions	
Chronic hypertension, n (%)	14 (14.9%)
Diabetes, n (%)	4 (4.3%)
HIV infection, n (%)	21(22.3%)
Blood pressure at presentation	
Systolic blood pressure (mmHg), mean (SD)	172.8 mmHg (30.1 mmHg)
Diastolic blood pressure (mmHg), mean (SD)	108.4 mmHg (15.8 mmHg)
Dipstix proteinuria on admission	
Mean (SD)	2.2+ (1.1+)
Average maternal weight at 1 year, mean (SD)	75.5 kg (22.1 kg)
Timing of delivery	
<34 weeks, n (%)	47 (50.0%)
34–37 weeks, n (%)	21 (22.3%)
>37 weeks, n (%)	26 (27.7%)
Number of days from admission to delivery, mean (SD)	4.2 (7.7)
Gestational age at delivery (weeks)	
Mean (SD)	32.1 (4.3)
Minimum	25.2
Maximum	41.3
Birthweight (grams)	
Mean (SD)	1954 (835.8)
Minimum	300
Maximum	3450
Biochemical markers on admission	
Haemoglobin (g/dl) mean (SD)	12.4 (2.1)
Platelets ($\times 10^9$/L) mean (SD)	116.7 (90.2)
Urea (mmol/L) mean (SD)	4.4 (3.6)
Creatinine (umol/L) mean (SD)	96.2 (50.4)
Aspartate Aminotransaminase mean (SD)	139.7 (195.0)

The incidence of HIV disease in the study population was 22.3%. The prevalence of WMLs was similar in the study population to that of the HIV uninfected group suggesting that HIV disease was not responsible for the development of WMLs. Fig. 1 compares the prevalence of WMLs at delivery, 6 months and 1 year between the study group and the HIV-uninfected sub-group of patients.

Thirty-four (36.2%) women had no WMLs on MRI while 41 (43.6%) demonstrated lesions on all studies (delivery, 6 months and 1 year). Seventeen (18.1%) women had lesions at delivery but the WMLs were no longer present at 1 year. Twelve out of seventeen of these women, whose lesions had regressed, were normotensive at 1 year. Four women did not have lesions at delivery but WMLs were present at the 1 year scan. Of these 4 women, 3 had chronic hypertension at 1 year. Fig. 2 illustrates the location of white matter lesions at delivery and 1 year. Five-percent and 2% of WMLs in the occipital and parietal lobes respectively, regressed. However there was a 7% increase in the number of lesions in the frontal lobes from delivery to 1-year postpartum.

Sixty-two percent of lesions were less than 3 mm in size, 36% were 3-10 mm and 2% were greater than 10 mm in size. Sixty-three (67.1%) patients were diagnosed with chronic hypertension at 1 year. Sixty-five percent (n = 42) of women with chronic hypertension at 1 year had WMLs compared with 32.3% (n = 10) of women who were normotensive (see Fig. 3).

Table 2 describes the independent predictors of outcome in relation to the presence of white matter lesions at 1 year. There was no significant association between the presence of cerebral WMLs and clinical presentation of HELLP syndrome, eclampsia or early onset disease. There was also no significant difference between the clinical variables and delivery <37 weeks.

Table 3 describes the relation between blood pressure variables and the presence of white matter lesions after 1 year. The number of drugs needed to control hypertension during the ante-natal period was significantly associated with the presence of WMLs after 1 year ($p < 0.0001$).

4. Discussion

Hypertension is a major contributor to a growing burden of non-communicable diseases and Africans, particularly young African women appear to be bearing the brunt of this increasing public health problem [22]. Compared to other racial groups, African women are at greater risk of developing pre-eclampsia with severe complications [23] Almost 95% of our study population was of African origin – this may explain the slightly higher prevalence of cerebral WMLs in our study at 1 year postpartum than the rates of 41%, 37% and 34.4% found in a predominantly Caucasian population more than 5 years after the index pregnancy in the studies by Aukes and Wiegman [19,20,24]. We found that the degree of hypertension rather than clinical variation of the pre-eclamptic process such as HELLP syndrome, eclampsia and early onset disease played a role in the development of WMLs. Aukes et al. also did not find any relation between the presence of HELLP syndrome, severe diastolic hypertension, neurological symptoms or the use or magnesium sulphate and the presence or severity of WMLs [12]. There was however a positive relation between early onset pre-eclampsia and current hypertension and the presence of WMLs in the study by Aukes [20].

A systematic review of 46 studies and *meta*-analysis has shown that white matter lesions are an important indicator of future risk of disease, being associated with an increased risk of stroke (hazard ratio 3.3, 95% CI 2.6–4.4), dementia (1.9, 95% CI 1.3–2.8) and death

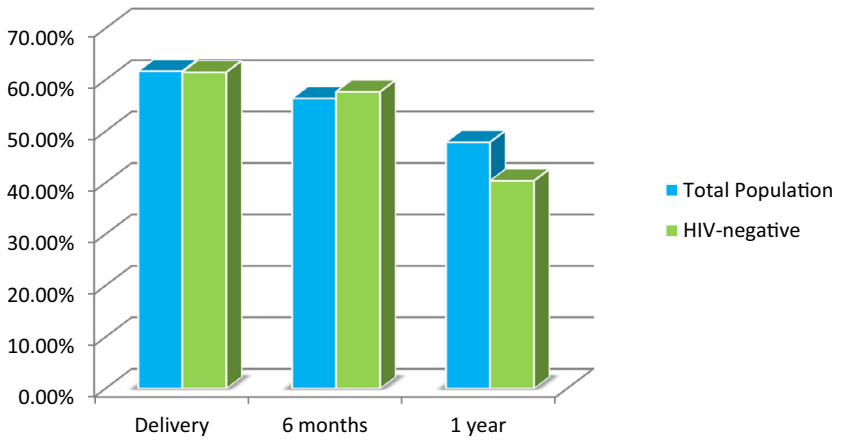

Fig. 1. Prevalence of lesions in study group compared with HIV-negative group.

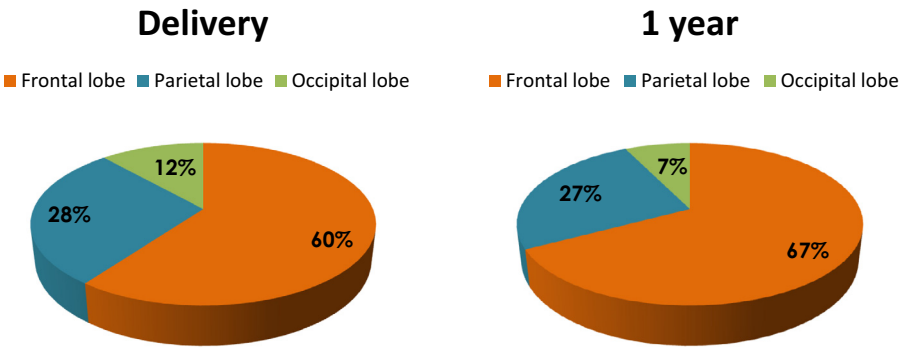

Fig. 2. Location of lesions at delivery and 1 year.

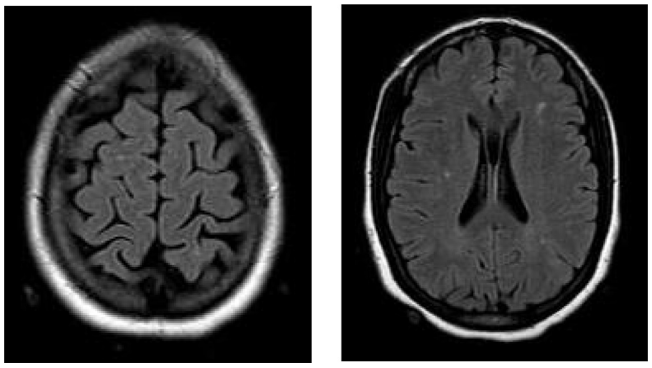

Fig. 3. Illustrates the white matter lesions in a pre-eclamptic woman at 1 year post-delivery.

(2.0, 95% CI 1.6–2.7) [15]. Almost half of the pre-eclamptic women in our study were found to have cerebral WMLs 1 year after delivery. The presence of WMLs was significantly associated with the number of drugs needed to control blood pressure during the ante-natal period (OR 5.1, 95% CI 2.3–11.3, $p < 0.0001$). The average time from admission to delivery in our study was 4.2 days. The MEXPRE Latin study found a significant increase in higher maternal morbidity (37.7% versus 14.3%, $p = 0.02$) in a group of pre-eclamptic women who were managed expectantly compared to prompt delivery group [25]. The authors found no neonatal benefit with a possible increased risk of abruption and small for gestational aged infants when women with severe pre-eclampsia were managed expectantly. Bombrys et al. reported a maternal complication rate of 27% among women with pre-eclampsia who were managed expectantly [26]. Complications included the development of HELLP syndrome, abruption placentae, pulmonary oedema and renal insufficiency. The authors concluded that although maternal morbidity was significant, all complications were reversible. Traditionally optimal management of severe pre-eclampsia depends on balancing the risks to the mother and fetus from pregnancy prolongation versus the risk of prematurity to the neonate from immediate delivery [26]. Expectant management of severe pre-eclampsia especially for those women requiring more than 1 drug to control hypertension is associated with increased risk of both short and long-term maternal morbidity

The pathophysiology of cerebral WMLs is presently uncertain but the distribution of the lesions may provide some insight. Currently 2 concepts regarding the pathophysiology have been proposed [19,20,24]. Aukes et al. have hypothesized that WMLs may be a complication of the posterior reversible encephalopathy syndrome(PRES) [19]. Oedema in PRES is typically located in the occipito-parietal lobes. White matter lesion distribution would therefore be expected primarily in the occipito-parietal areas of the brain. We found that WMLs were already present at delivery and furthermore majority of the lesions (60%) were located in the frontal lobes. This is consistent with the findings of Wiegman et al. who in a follow-up of pre-eclamptic patients found that 85% of the lesions were in the frontal lobes, 35% in the parietal lobes and 11% in the temporal lobes [24]. We therefore support the suggestion by Wiegman et al. that a direct causal relationship between the cerebral oedema of PRES and WMLs is unlikely. According to the vasculopathy theory, severe hypertension leads to cerebral overregulation and vasospasm [19]. Cerebral small ves-

Table 2
Relationship between the clinical picture at delivery and the presence of WMLs at 1 year.

	1 year		*Total*	*P-value*
Potential predictors	**No WMLS n (%)**	**WMLS N (%)**		
Uncomplicated pre-eclampsia	13 (27.7%)	13 (27.7%)	26 (27.7%)	
Delivery <34 weeks	8 (17.0%)	7 (14.9%)	15 (16.0%)	
Eclampsia	3 (6.4%)	4 (8.5%)	7 (7.4%)	
Eclampsia & delivery <34 weeks	4 (8.5%)	6 (12.8%)	10 (10.6%)	P = 0.9
HELLP	6 (12.8%)	3 (6.4%)	9 (9.6%)	
HELLP & delivery <34 weeks	10 (21.3%)	11 (23.4%)	21 (22.3%)	
HELLP & eclampsia	3 (6.4%)	2 (4.3%)	5 (5.39%)	
HELLP & eclampsia & delivery <34 weeks	0 (0.0%)	1 (2.1%)	1 (1.1%)	
Total	**47 (100.0%)**	**47 (100.0%)**	**94 (100.0%)**	

Table 3
Univariate analysis of blood pressure- related variables.

Blood pressure variable	Absence of WML	Presence of WML	P-Value
Mean arterial BP(mmHg)	141.9 (21.4)	140.5 (19.3)	0.75
Episodes of severe hypertensive days			
Median	1.00	1.0	0.9
Minimus	0	0	
Maximus	5.0	10.0	
Episodes of low blood pressure			
Median	0.0	0.0	0.6
Minimum	0.0	0.0	
Maximum	2.0	2.0	
Number of drugs needs to control BP			
Mean (SD)	1.28 (0.9)	2.2 (0.7)	< 0.0001
Median (range)	1 (0–3)	2.0 (1–3)	
No of episodes of severe HT (greater than160/110 mmHg)			
Median	2.0	2.0	
Minimum	0.0	0.0	0.7
Maximum	7.0	10.0	
No of days from admission to delivery			
Median	1.0	1.0	0.3
Minimum	0	0	
Maximum	97.0	31.0	
BMI at booking mean (SD)	30.0	31.1	0.5

sel disease is the term used to describe the clinical, cognitive and neuroimaging findings resulting from an intrinsic process affecting small cerebral arterioles, capillaries and venules [27]. The key mechanism underlying brain injury secondary to small vessel disease is ischemia which results from narrowed arteries or structural or functional occlusion [27]. The vessel lumen restriction is believed to result in a state of chronic hypoperfusion of white matter, eventually resulting in degeneration of myelinated fibres [28]. This mechanism of white matter damage is the result of an incomplete infarct or selective necrosis [29]. Acute occlusion of a small vessel will lead to focal and acute ischemia and complete tissue necrosis [28]. Other mechanisms that are believed to contribute to ischemic forms of small vessel disease are blood-brain barrier damage, local subclinical inflammation and oligodendrocyte apoptosis [28]. The association between current hypertension in the study by Aukes and the number of drugs needed to achieve adequate blood pressure control in our study and the persistent presence of WMLs therefore supports the theory that hypertension per se rather than variations in clinical presentation of pre-eclampsia possibly plays a role in the development of WMLs. It is also likely that these lesions developed during the ante-natal period prior to delivery.

Several studies have shown that women with pre-eclampsia have an increased risk of chronic hypertension in future life (RR 3.70; 95% CI 2.70–5.05) [30]. The incidence of chronic hypertension 1 year after delivery in our study population, who had a mean age of 28 years, was 61%. This is higher than the rates reported in retrospective studies by Habli (33% over a 5 year mean follow-up period) and Sibai (6.2%) [31,32]. This increased rate of chronic hypertension in our study is most likely because almost 95% of our study population was of African origin. A Nigerian study has found that not only do Africans develop more hypertension compared to other groups but hypertension is also more severe and resistant to treatment [33]. In the general population, hypertension increases the risk for the development of WMLs. A prospective, population-based study among elderly patients has found that current hypertension and hypertension established more than 5 years previously are associated with WMLs in the subcortical and periventricular regions [17] Furthermore high systolic blood pressure and high diastolic blood pressure is associated with WML progression [18]. This may explain the increased prevalence of WMLs (65.1% vs 32.3%) in women with chronic hypertension compared to those women who were normotensive.

Twelve out of 17 women whose blood pressure had normalised after delivery showed regression of lesions. Studies in the ageing population particularly patients with long-standing chronic hypertension have not shown any regression of lesions. There are however studies that have shown that in acute conditions of severe pre-eclampsia and eclampsia the clinical findings and radiologic abnormalities occurring in PRES resolve almost completely after restoration of normal blood pressure [6,8]. Similarly, a case-report of 2 non-pregnant adults and a child with hypertensive encephalopathy reported reversal of WMLs 4–5 weeks after initial studies [34]. The authors of this case-report stated that hypertensive encephalopathy is caused by multifocal extravasation of fluid and proteins across the blood-brain barrier during break-through of cerebral autoregulation [34]. Furthermore the high-intensity lesions seen on MRI are reflections of this protein and fluid extravasation and that resolution of lesions reflect their reabsorp-

tion [34]. This may explain the regression of some lesions in our study, particularly those in the occipital regions which may suggest that lesions in the occipital lobes are the consequence of PRES.

The strength of this study was that this is the first paper to show that in women with severe pre-eclampsia, WMLs most likely develop during the ante-natal period and that lesions that persist are unlikely the consequence of PRES. A possible limitation of the study is that most patients were seen for the first time during pregnancy with severe acute hypertension. Only 14.9% of women were known with chronic hypertension. It is possible that some women had undiagnosed chronic hypertension – this is especially likely as the rate of chronic hypertension postpartum was 61%. A further limitation of the study is that only a select group of pre-eclamptic patients were recruited to the study and relation between the WMLs and neurocognitive function was not evaluated.

5. Conclusion

Women who develop pre-eclampsia during pregnancy have an increased risk of developing cerebral white matter lesions after delivery. This risk is further increased in women who require 2 or more drugs to control blood pressure during pregnancy and those who develop chronic hypertension after the pregnancy.

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Cardiovascular Topics

Cardiac diastolic function after recovery from pre-eclampsia

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Abstract

Background: Pre-eclampsia is associated with significant changes to the cardiovascular system during pregnancy. Eccentric and concentric remodelling of the left ventricle occurs, resulting in impaired contractility and diastolic dysfunction. It is unclear whether these structural and functional changes resolve completely after delivery.

Aims: The objective of the study was to determine cardiac diastolic function at delivery and one year post-partum in women with severe pre-eclampsia, and to determine possible future cardiovascular risk.

Methods: This was a descriptive study performed at Steve Biko Academic Hospital, a tertiary referral hospital in Pretoria, South Africa. Ninety-six women with severe pre-eclampsia and 45 normotensive women with uncomplicated pregnancies were recruited during the delivery admission. Seventy-four (77.1%) women in the pre-eclamptic group were classified as a maternal near miss. Transthoracic Doppler echocardiography was performed at delivery and one year post-partum.

Results: At one year post-partum, women with pre-eclampsia had a higher diastolic blood pressure (p = 0.001) and body mass index (p = 0.02) than women in the normotensive control group. Women with early onset pre-eclampsia requiring delivery prior to 34 weeks' gestation had an increased risk of diastolic dysfunction at one year post-partum (RR 3.41, 95% CI: 1.11–10.5, p = 0.04) and this was irrespective of whether the patient had chronic hypertension or not.

Conclusion: Women who develop early-onset pre-eclampsia requiring delivery before 34 weeks are at a significant risk of developing cardiac diastolic dysfunction one year after delivery compared to normotensive women with a history of a low-risk pregnancy.

Keywords: pre-eclampsia, diastolic function, left ventricular remodelling, pregnancy

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Pre-eclampsia is a pregnancy-specific disorder characterised by new-onset hypertension and proteinuria after 20 weeks' gestation. Hypertensive disorders in pregnancy have been one of the top five causes of maternal mortality in South Africa for more than a decade.[1] It was previously believed that the complications of pre-eclampsia ended with the delivery of the foetus and placenta, however it is now well established that pre-eclampsia is a risk for future hypertension, ischaemic heart disease, stroke and venous thromboembolism.[2]

Pregnancy is associated with significant haemodynamic and hormonal changes affecting the cardiovascular system. There is a 20% increase in cardiac output by eight weeks' gestation.[3] Peripheral vasodilatation leads to a 20 to 30% fall in systemic vascular resistance and a 40% increase in cardiac output. The heart undergoes remodelling, with an increase in left ventricular wall thickness and mass.[4]

Despite these changes, the left ventricular contractile function is maintained and any changes in cardiac geometry are rapidly reversible within three months post-partum in normotensive women.[4] By contrast, vascular reactivity is augmented in pregnancies affected by pre-eclampsia.[5] Pre-eclampsia results in a state of increased vascular stiffness, generalised vasoconstriction and a high total vascular resistance and low cardiac output compared to the changes seen in a normal pregnancy. [5]

Cardiac changes classically associated with pre-eclampsia are diastolic dysfunction and an after-load-mediated left ventricular remodelling of the maternal heart.[6-8] The heart remodelling is a response to the increased systemic afterload in order to minimise myocardial oxygen demand and preserve left ventricular function.

About 20% of women with pre-term pre-eclampsia and severe disease undergo severe left ventricular hypertrophy with advanced cardiac dysfunction.[9] Typically there is preservation of both left atrial geometry and function, and left ventricular systolic function.[4,10] The right ventricle is also usually unaffected.[10] Levels of brain naturetic peptide (BNP) increase in pregnancies

complicated by pre-eclampsia, and Fayers *et al.* have shown that the increase in BNP is accompanied by changes in left ventricular diastolic function.[11] Elevated BNP levels are possibly the result of myocardial remodelling and sub-clinical ventricular dysfunction that accompanies the severe vasoconstriction observed in pre-eclampsia.[11]

Diastolic dysfunction is described as impaired left ventricular filling and may be present in the setting of normal or abnormal systolic function. Pre-clinical diastolic dysfunction is associated with the development of future heart failure and is a predictor of all-cause mortality.[12] Diastolic filling abnormalities may also play a significant role in the pathogenesis of pulmonary oedema, complicating hypertensive crises in pregnancy.[13]

Desai *et al.* found that diastolic filling abnormalities were demonstrated in a significant proportion of pre-eclamptic pregnancies complicated by pulmonary oedema compared to control groups of women who were hypertensive and normotensive in pregnancy.[13] The authors of this study postulated that the diastolic filling abnormalities demonstrated in the study occurred within a short time frame of severe pre-eclampsia in pregnancy or could represent pre-eclampsia superimposed on established hypertension.

Whether diastolic dysfunction persists after delivery is uncertain. Identifying factors that may affect future cardiovascular risk may identify a group of women requiring increased post-partum vigilance and lifestyle modification. The aim of this study was to determine cardiac diastolic function at delivery and one year post-partum in women with severe pre-eclampsia and to further determine possible future cardiovascular risk.

Methods

This was a descriptive study of women with severe pre-eclampsia, performed at Steve Biko Academic Hospital from 1 April 2013 to 30 March 2016. The Cardiology Department at Steve Biko Academic Hospital reserved echocardiographic appointments every Wednesday during the study period. Post-partum women with severe pre-eclampsia were identified on a Wednesday morning and if fit to be transported to the cardiology clinic, were informed of the study. Echocardiographic studies were performed on patients who consented to the procedure and were agreeable to follow-up studies.

One hundred and six women with severe pre-eclampsia and 45 normotensive, low-risk women who served as the control group

Table 1. Utility, advantages and limitations of variables used to assess left ventricular diastolic function[15] (reproduced with permission)

Variable	*Physiological background*	*Advantages*	*Limitations*
Mitral E velocity	Reflects the LA–LV pressure gradient during early diastole and is affected by alterations in the rate of LV relaxation and LAP	Feasible and reproducible	Directly affected by alterations in LV volumes and elastic recoil. Age dependent
Mitral A velocity	Reflects the LA–LV pressure gradient during late diastole, which is affected by LV compliance and LA contractile function	Feasible and reproducible	Sinus tachycardia, first-degree AV block and paced rhythm can result in fusion of the E and A waves. If mitral flow velocity at the start of the atrial contraction is > 20 cm/s, A velocity may be increased. Age dependent
Mitral E/A ratio	Mitral inflow E/A ratio and DT are used to identify the filling patterns	Feasible and reproducible. Provides diagnostic and prognostic information. A restrictive filling pattern in combination with LA dilatation in patients with normal EFs is associated with a poor prognosis similar to a restrictive pattern in dilated cardiomyopathy	The U-shaped relationship with LV diastolic function makes it difficult to differentiate normal from pseudonormal filling, particularly with normal LVEF, without additional variables. If mitral flow velocity at the start of atrial contraction is > 20 cm/s, E/A ratio will be reduced due to fusion. Age dependent
Mitral E-velocity DT	DT is influenced by LV relaxation, LV diastolic pressures following mitral valve opening, and LV stiffness	Feasible and reproducible. A short DT in patients with reduced LVEF indicates increased LVEDP with high accuracy both in sinus rhythm and in AF	DT does not relate to LVEDP in normal LVEF. Should not be measured with E and A fusion due to potential inaccuracy. Age dependent
Pulsed-wave TDI-derived mitral annular early diastolic velocity: e′	A significant association is present between e′ and the time constant of LV relaxation shown in both animals and humans. The haemodynamic determinants of e′ velocity include LV relaxation, restoring forces and filling pressure	Feasible and reproducible. LV filling pressures have a minimal effect on e′ in the presence of impaired LV relaxation. Less load dependent than conventional blood-pool Doppler parameters	Need to sample at least two sites with precise location and adequate size of sample volume. Different cut-off values depending on the sampling site for measurement. Age dependent
Mitral E/e′ ratio	e′ velocity can be used to correct for the effect of LV relaxation on mitral E velocity, and E/e′ ratio can be used to predict LV filling pressures	Feasible and reproducible. Values for average E/e' ratio < 8 usually indicate normal LV filling pressures, values > 14 have high specificity for increased LV filling pressures	E/e′ ratio is not accurate in normal subjects, patients with heavy annular calcification, mitral valve and pericardial disease. 'Gray zone' of values in which LV filling pressures are indeterminate. Different cut-off values depending on the sampling site for measurement

LV, left ventricular; LA, left atrial; LAP, left atrial pressure; LVEF, left ventricular ejection fraction; DT, mitral E-velocity deceleration time; e′, lateral early diastolic velocity; AF, atrial fibrillation.

were identified and recruited shortly after delivery. Women with structural heart disease or pulmonary embolus were excluded from the study. Women diagnosed with maternal metabolic syndrome were not recruited to the control group.

Echocardiograms of the maternal heart were performed between day two and seven post-delivery and follow-up scans were done after one year. Hypertensive disorders were classified according to the classification and diagnosis of the International Society for the Study of Hypertension in Pregnancy (ISSHP).[14]

Doppler echocardiography was carried out by the Department of Cardiology at Steve Biko Academic Hospital. The following echocardiographic parameters were assessed in the evaluation of diastolic dysfunction: left ventricular ejection fraction (LVEF), mitral E-wave (E) and mitral A-wave velocities (A), E/A ratio, mitral E-velocity deceleration time (DT), lateral early diastolic (e′) velocity tissue Doppler and E/e′ ratio.

The diagnosis of diastolic dysfunction was made by a clinician in the cardiac-obstetric unit. All women diagnosed with diastolic dysfunction had the following minimum positive criteria: average E/e′ > 14 and lateral e′ velocity < 10 cm/s. The American Society of Echocardiography and the European Association of Cardiovascular Imaging have described the advantages and limitations used to assess left ventricular diastolic function[15] (Table 1).

Descriptive statistics in the form of means and standard deviations in the case of continuous data, and frequencies and percentages in the case of categorical data were calculated. A *p*-value of < 0.05 was considered significant. Ethical approval for the study was obtained from the University of Pretoria Ethics Committee (No. 125/2013).

Table 2. Demographic data of the study population

Characteristics	*Pre-eclamptic group (n = 96)*	*Control group (n = 45)*	p-*value*
Age, years			
Mean (SD)	28.9 (6.83)	27.2 (7.14)	0.66
Range	18–46	20–42	
Race			
African, *n* (%)	86 (89.58)	38 (84.44)	
Caucasian, *n* (%)	5 (5.20)	3 (6.67)	
Coloured, *n* (%)	4 (4.17)	4 (8.89)	
Indian, *n* (%)	1 (1.04)	0 (0)	
Obstetric history			
Parity mean (range)	1.3 (0–4)	1.6 (0–5)	
Timing of delivery			
< 34 weeks, *n* (%)	44 (45.83)	0 (0)	
34–37 weeks, *n* (%)	25 (26.04)	5 (11.11)	
> 37 weeks, *n* (%)	27 (28.13)	40 (88.89)	
Medical conditions			
Diabetic at 1 year, *n* (%)	6 (6.25)	0 (0)	
Hypertensive at 1 year, *n* (%)	52 (54.17)	2 (4.44)	
Haemoglobin at 1 year (g/dl)			
Mean (SD)	12.02 (1.46)	12.42 (1.13)	0.15
Blood pressure at 1 year (mmHg)			
Systolic, mean (SD)	128.01 (14.17)	115.08 (9.89)	0.08
Diastolic, mean (SD)	80.91 (14.47)	72.45 (9.16)	0.001
BMI at 1 year, mean (SD)	30.27 (7.55)	28.04 (3.64)	0.02

Results

There were 6 536 deliveries at our hospital during the recruitment phase of the study (1 April 2013 – 30 March 2015). Four hundred and sixty-three (7.1%) women presented with severe pre-eclampsia and 106 women were recruited to the study. Ten women were lost to follow up. Data were therefore recorded for 96 women with severe pre-eclampsia and 45 controls.

Seventy-four (77.1%) women in the study group for whom data were available fulfilled the World Health Organisation (WHO) criteria for the classification of a maternal near miss. Of the 96 women with severe pre-eclampsia, 14 were diagnosed with chronic hypertension and four with diabetes prior to pregnancy. At one year, the mean diastolic blood pressure and mean body mass index was significantly higher among the women who had pre-sclampsia during pregnancy compared to the normotensive control group. Table 2 describes the demographic data of the study population.

Twenty women (20.83%) with pre-eclampsia were diagnosed with diastolic dysfunction at delivery compared with six (13.3%) of the controls ($p = 0.26$). Of the 20 women who were diagnosed with diastolic dysfunction at delivery, 13 (65%) had early-onset pre-eclampsia, requiring delivery prior to 34 weeks. At one year, 11 (11.46%) women with pre-eclampsia were diagnosed with diastolic dysfunction compared with three (6.67%) in the control group. (RR = 1.67; $p = 0.27$).

Women with early-onset pre-eclampsia requiring delivery prior to 34 weeks' gestation had an increased risk of diastolic dysfunction at one year post-partum (RR 3.41, 95% CI: 1.11–10.5, $p = 0.04$) (Fig. 1). Delivery prior to 34 weeks was associated with an increased risk of diastolic dysfunction even if patients with chronic hypertension at one year were excluded from the analysis ($p = 0.02$, 95% CI: 1.43–97.67) There was no significant association between diastolic dysfunction and chronic hypertension at one year (RR = 2.02, $p = 0.33$, 95% CI: 0.57–7.13). Echocardiographic measurements of diastolic function after one year are shown in Table 3.

Left ventricular systolic function was normal and similar in both groups, suggesting preservation of systolic function in both pre-eclamptics and controls. There was a significant decrease in lateral e′ and a significant increase in A velocity between the pre-eclamptic and control group at one year.

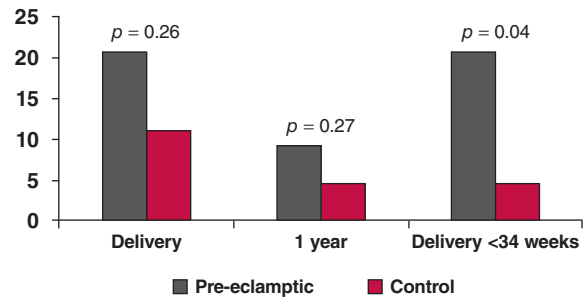

Fig. 1. Risk of diastolic dysfunction at delivery and at one year, and at one year for sub-group of women with early-onset pre-eclampsia requiring delivery prior to 34 weeks.

Table 3. Cardiac diastolic function at one year

	Pre-eclamptic group, mean (SD)	*Control group, mean (SD)*	p-*value*
Left ventricular ejection fraction, %	60.54 (7.62)	63.43 (4.88)	0.08
E velocity, m/s	0.98 (0.20)	0.95 (0.14)	0.90
A velocity, m/s	0.70 (0.24)	0.64 (0.05)	0.01
E/A ratio	1.42 (0.39)	1.46 (0.12)	0.74
E-deceleration time (ms)	224.57 (51.00)	225.43 (35.09)	0.08
Lateral e′ (cm/s)	10.83 (2.86)	11.80 (1.99)	0.02
E/e′ ratio	10.11 (5.32)	9.96 (2.25)	0.11

Discussion

Heart failure is a progressive condition, which begins with risk factors for left ventricular dysfunction and progresses further to asymptomatic changes in cardiac structure and function, finally evolving into heart failure.[16] Myocardial remodelling starts before the onset of symptoms. Diastolic dysfunction precedes the onset of systolic dysfunction in 50% of cardiac diseases, which further precedes the onset of heart failure.[5]

The American College of Cardiology has highlighted the importance of identifying asymptomatic cardiac dysfunction for early intervention and improvement of outcome.[17] The risk for left ventricular diastolic dysfunction is significantly associated with higher age, body mass index (BMI), heart rate and systolic blood pressure.[16] The prevalence of diastolic dysfunction in a general population aged less than 49 years was found to be 6.8%, and 27.3% for the total population, which included study subjects older than 70 years.[16]

Zanstra *et al*. found that 24% of women with the metabolic syndrome during pregnancy had diastolic dysfunction at six months post-partum, compared to 6.3% of women with low-risk pregnancies.[18] Obesity and diastolic hypertension were strong correlates to diastolic dysfunction.

The rate of diastolic dysfunction at one year in the two groups of women with early-onset pre-eclampsia (22.7%) and low-risk pregnancies (6.7%) in our study were similar to rates reported by Zanstra *et al.*[16] Although our study did not find associations between diastolic blood pressure and obesity with diastolic dysfunction, women in the pre-eclamptic group had a significantly higher BMI and diastolic blood pressure than those in the control group. Additionally, diastolic dysfunction is also a risk factor for future death.

The Olmsted study described the predictive significance of left ventricular diastolic dysfunction using multivariable-adjusted analyses.[19] The hazard ratio for all-cause mortality was 8.31 ($p < 0.001$) for mild diastolic dysfunction and 10.17 for moderate to severe diastolic dysfunction ($p < 0.001$). At one year post-delivery, diastolic dysfunction was present in 11.5% of women with pre-eclampsia, in 22.7% of women with early-onset pre-eclampsia and in 1.9% of women whose pre-eclampsia developed after 34 weeks. Women with early-onset pre-eclampsia requiring delivery prior to 34 weeks, irrespective of the presence of chronic hypertension, were at risk of developing diastolic dysfunction at one year post-delivery. Chronic hypertension, therefore, was not an additional risk factor for diastolic dysfunction at one year in women with early-onset pre-eclampsia.

This study found that early-onset pre-eclampsia was a risk factor for diastolic dysfunction, while women who developed pre-eclampsia after 34 weeks had a risk similar to that of low-risk parous women (RR 3.41, 95% CI: 1.11–10.5, $p = 0.04$). This may be explained by the proposed differences in pathophysiology between early- and late-onset pre-eclampsia.

Redman *et al.* have suggested that pre-eclampsia could be the result of intrinsic or extrinsic placental causes.[20] In early-onset pre-eclampsia, factors extrinsic to the placenta affect the uteroplacental circulation via incomplete spiral artery remodelling, while in late-onset disease, intrinsic factors affect the size of the placenta, restricting intervillous perfusion.[20]

The placentas of women with early-onset disease differ significantly from those who develop pre-eclampsia at term.[21] The former group demonstrate placental findings consistent with insufficiency and vascular lesions, while late-onset disease is characterised by placental hyperplasia and unimpaired foetal growth.[21-24] Further evidence suggesting that pre-eclampsia is more than one disease comes from differences in biochemical markers, Doppler studies and clinical features of the disease.[25-30]

Pre-eclampsia is a known risk factor for future chronic hypertension. Hypertension and hypertensive heart disease are one of the key contributors to the burden of non-communicable cardiovascular disease in Africa. Young African women are bearing the brunt of this increasing public health problem.[31,32] Several studies have found that women from sub-Saharan Africa have the greatest risk of developing pre-eclampsia and eclampsia.[33,34]

Nakimuli *et al*., in a study of pre-eclampsia in women of African ancestry, found that African ancestry was the second strongest risk factor for pre-eclampsia after chronic hypertension.[35] African ancestry was also a risk factor for early-onset pre-eclampsia and poor obstetric outcomes such as foetal growth restriction and stillbirth.[35] Pregnancy-related deaths from pre-eclampsia are also three times higher in women of African ancestry compared with Europeans.[36] Almost 90% of women in our study were of African origin.

It is estimated that for every woman who dies during pregnancy or childbirth, 20 others will suffer severe morbidity.[37] Most maternal mortality and morbidity datasets record information for up to 42 days post-partum. However women who develop pre-eclampsia during pregnancy, especially those with early-onset disease, may develop heart failure several years after pregnancy, resulting in the problem not being adequately identified and addressed.

The prognosis of women with compromised cardiac function is poorer than that of men.[18] Women often present with atypical symptoms, resulting in delayed presentation, delayed diagnosis and suboptimal care compared to men.[38,39] These factors highlight the need to identify women at risk of future cardiovascular disease, with the aim of reducing potential modifiable risk factors. Blood pressure control, weight loss and a low-sodium diet are important measures that have been identified with favourable changes in ventricular diastolic function.[18] The American Heart Association Guideline on Lifestyle Management to reduce cardiovascular risk for adults who would benefit from blood pressure lowering include dietary modification appropriate to calorie requirements, reduction in salt intake and three to four sessions of aerobic activity per week lasting on average 40 minutes per session.[40]

This is the first study to evaluate diastolic function in a pre-eclamptic group of predominantly African population. Although we did not look at other risk factors for cardiovascular disease in this population, the study provides valuable information in identifying a potential group of women at risk of disease at an early stage. This would provide opportunities for screening and lifestyle modification.

The strength of this study is that it is one of the first to look at cardiac diastolic function in an African population where the rates of hypertension both during and outside of pregnancy were high. A possible limitation is that most patients were seen for the first time during pregnancy, with severe acute hypertension. Only 14.6% of women were known to have chronic hypertension. It is possible that some women had undiagnosed chronic hypertension – this is especially likely as the rate of chronic hypertension postpartum at one year was 54.2%. Some of the women with undiagnosed chronic hypertension may have had pre-existing diastolic dysfunction that could have been worsened by the superimposed pre-eclampsia. A further limitation is that only a select group of pre-eclamptic women were recruited to the study.

Conclusion

Women who develop early-onset pre-eclampsia requiring delivery prior to 34 weeks' gestation have an increased risk of cardiac diastolic dysfunction one year after delivery. Diastolic dysfunction precedes the onset of systolic dysfunction and clinical heart failure. A strategy to screen and treat women with cardiovascular risk, particularly in lower- and middle-income countries should be explored further.

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The effect of pre-eclampsia on retinal microvascular caliber at delivery and post-partum

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Abstract

Background: The retinal microcirculation provides a unique view of microvessel structure by means of non-invasive, retinal image analysis. The aim of the study was to compare the retinal vessel caliber at delivery and one-year post-partum between women who have had pre-eclampsia during pregnancy to a normotensive control group.

Methods: Digital photos of the eye were taken at delivery and one-year post-partum. Retinal vessels were analysed and summarised as the corrected central retinal arteriolar equivalent and corrected central retinal venular equivalent.

Results: The corrected central retinal arteriolar equivalent and corrected central retinal venular equivalent were significantly lower in the pre-eclamptic group compared to the control group both at delivery and one-year post-partum ($p < 0.001$).

Conclusion: Retinal artery and venular caliber changes that occur during pregnancies affected by pre-eclampsia persist for up to one-year post-partum. These changes may reflect a permanent, long-term microvascular dysfunction and may be useful as a biomarker of future vascular risk.

Keywords

Retinal microvascular calibre, pre-eclampsia, hypertension

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Introduction

Pre-eclampsia is a pregnancy-specific disorder characterised by new onset hypertension after 20 weeks' gestation. Although the pathogenesis of pre-eclampsia is still poorly understood, it is well recognised that the disease contributes to gross maternal vascular dysfunction.[1] Endothelial dysfunction, resulting in increased peripheral resistance, is an integral part of the maternal syndrome. The ischemic placenta releases a number of pro- and anti-angiogenic factors and inflammatory markers into the maternal circulation. These factors are critical in mediating vascular function.[2] Vessels of women with pre-eclampsia show hypersensitivity to vasopressors and decreased response to vasodilators and vascular levels of vasodilators such as nitric oxide and prostacyclin are reduced in women with pre-eclampsia.[2 6]

The degree of dilatation and constriction of the retinal microvasculature during normal pregnancy have been shown to correlate with the physiological changes in the mean arterial blood pressure (MAP).[7] Differences in retinal microvasculature are believed to reflect cerebrovascular changes and are associated with systemic changes in vascular response.[8] The retinal microcirculation provides a unique view of microvessel structure by means of non-invasive, image analysis.[8] Retinal imaging primarily measures retinal microvessel caliber and retinal vessel caliber is relatively stable in healthy individuals with only subtle constriction for each decade increase in age.[9]

Lupton et al. compared the changes in retinal microvessel caliber during pregnancy between women who had a normotensive pregnancy to those who subsequently developed pre-eclampsia.[10] The central retinal arteriolar equivalent corrected for mean blood pressure (cCRAE) was significantly lower at term in the pre-eclamptic group compared to women who were normotensive during pregnancy. In general populations, such narrowing of retinal arteriolar caliber has been associated with increased risk of severe hypertension and stroke.[11,12] However it is uncertain whether changes in retinal arteriolar vessel caliber during pregnancies complicated by pre-eclampsia recover after delivery of the fetus and placenta or persist beyond the immediate post-partum period and whether such changes may be markers of future risk. There have been studies showing that women with a history of pre-eclampsia are more likely to develop hypertension and cardiovascular disease in later life.[13,14]

The aim of this study was to compare the retinal vessel caliber at delivery and one-year post-partum between women who have had pre-eclampsia during pregnancy to a normotensive control group.

Methods

This was a case control study of women with severe pre-eclampsia at Steve Biko Academic Hospital, a tertiary referral hospital in Pretoria South Africa, from 1 April 2013 to 30 March 2016. This study formed part of a larger study of pre-eclamptic women which included the evaluation of cardiac diastolic function using echocardiography and the investigation for the presence of cerebral white matter lesions (WMLs) by magnetic resonance imaging (MRI). Recruitment of patients took place from 1 April 2013 to 30 March 2015 and follow-up visits took place from 1 April 2014 to 30 March 2016. Post-partum women (days 2 7 post-delivery) with severe pre-eclampsia were identified every morning during the labour ward round. Women were

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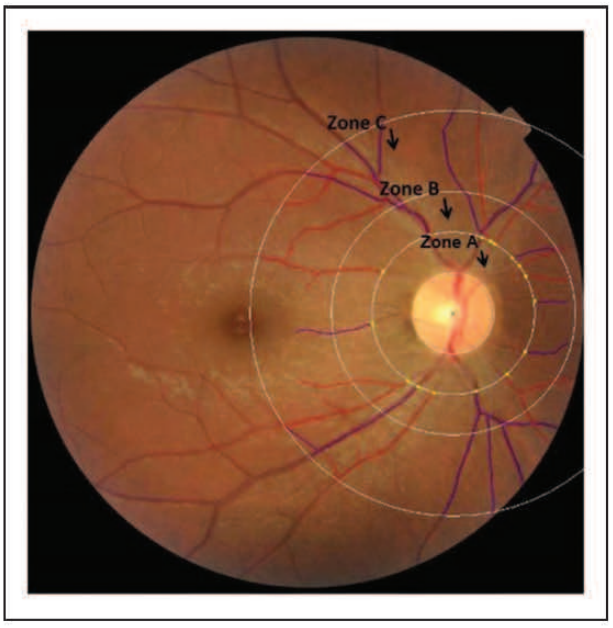

Figure 1. Digitised retinal photograph. Zone B is a half-disc to one and half disc diameter from the optic disc margin. Retinal vessel diameter measurements were performed in Zone B.

informed of the study if they were fit to be transported to various departments in the hospital for imaging studies. Retinal images were collected at delivery and one-year post-partum in patients who also consented to undergoing echocardiography and MRI imaging at delivery and were agreeable to follow-up visits. Normotensive women who had uncomplicated pregnancies served as the control group. Hypertensive disorders were classified according to the classification and diagnosis of the International Society for the Study of Hypertension in Pregnancy (ISSHP).[15]

Retinal imaging was performed using the Topcon TRC-NW8 45^0 non-mydriatic retinal fundus camera. Photographs were taken between day 2 7 post-delivery and at one-year post-partum. Women were rested for a few minutes in a dark room before photography to achieve pupil dilatation without pharmacological mydriasis. Macula-centred digital photographs of both fundi were taken. The right eye was chosen for analysis because retinal vessel characteristics are comparable between the right and left eyes.[16] Photographs were graded at the Singapore Eye Research Institute. Retinal image graders were blinded to the clinical information of the study patients. Images were graded using a semi-automated retinal vascular caliber measurement software program. Digital retinal images can be divided into standardised areas around the optic disc for repeatable analysis.[17] The areas around the optic disc are divided into the following zones (Figure 1):

Zone A ½ optic disc diameter from the disc margin
Zone B Edge of zone A to 1 disc diameter from the optic disc margin
Zone C Edge of zone B to 2 disc diameter from optic disc margin

It has been suggested that the smaller retinal vessels which are furthest away from the optic disc are more affected by hypertension.[18] Zone B, which has larger vessels is chosen as the standard area of analysis. Retinal vascular caliber was assessed using a standardised protocol based on the revised Knudtson Parr Hubbard formula.[18] Retinal arteriolar and venular calibers were summarised using the six largest arterioles and the six largest venules as the central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE) respectively.

The MAP was calculated using the formula $MAP = DP + 1/3(SP - DP)$, where DP and SP represent systolic and diastolic blood pressure respectively. The effect of blood pressure on retinal vessel calibre was corrected by dividing the CRAE and CRVE by the MAP to produce the cCRAE and cCRVE respectively.[19] Descriptive statistics in the form of means and standard deviations was performed. Univariate analysis comparing women with pre-eclampsia and the control group at delivery then one-year were performed making use of independent sample t-tests. A p-value of <0.05 was considered statistically significant. Ethical approval for the study was obtained from the University of Pretoria Research Ethics Committee (No. 125/2013).

Table 1. Demographic data of the study population.

	Pre-eclamptic group (n = 40)	Control group (N = 40)
Age, years		
Mean (SD)	29.3 (6.4)	29.1 (7.5)
Range	17–41	18–46
Race		
African, n (%)	35 (87.5)	35 (87.5)
Caucasian, n (%)	2 (5.0)	3 (7.5)
Coloured, n (%)	2 (5.0)	2 (5.0)
Indian, n (%)	1 (2.5)	0
Timing of delivery		
<34 weeks, n (%)	25 (62.5)	0
>34 weeks, n (%)	15 (37.5)	40 (100.0)
Mean birth weight		
Grams, (SD)	1893 (842.1)	3192 (342.8)
Medical conditions		
Diabetic at one year, n (%)	2 (5.0)	0
Hypertensive at one year, n (%)	22 (55.0)	1 (2.5)
MAP (mmHg) at delivery mean (SD)	111.73 (7.52)	88.78 (7.44)
MAP (mmHg) at one year mean (SD)	100.50 (15.22)	89.92 (7.88)

MAP: mean arterial blood pressure.

Results

There were 6536 deliveries at Steve Biko Academic Hospital during the recruitment phase of the study (1 April 2013 30 March 2015). Four hundred and sixty-three (7.1%) women presented with severe pre-eclampsia and 106 women were recruited to the larger study (described in the Methods section). Seven women were lost to follow-up and five declined testing at different stages of the study. Data were therefore available for 94 patients. Seventy-three (77.7%) women for whom data were available fulfilled the World Health Organisation (WHO) criteria for the classification of a maternal near miss.[20] Research funding was available for grading of 160 digital photographs. Forty pairs of the best quality digital fundus photographs, at delivery and one-year post-partum, were selected from the pre-eclamptic and control study groups for grading at the Singapore Eye Research Institute. Fifty-five percent (n = 22) of women in the pre-eclamptic group were diagnosed with chronic hypertension at one year. There was a statistically significant difference in the MAP between the pre-eclamptic and control groups at delivery and one year ($p < 0.001$). The demographic data of the study population are described in Table 1.

Table 2. Comparison between the retinal artery and vein calibre between the pre-eclamptic and control groups at delivery and one year.

	Pre-eclamptic group (n = 40)	Control group (n = 40)	*p*-value
Delivery			
MAP (mmHG) mean (SD)	111.73 (7.52)	88.76 (7.44)	$p < 0.001$
cCRAE (μm) mean (SD)	1.00 (0.15)	1.30 (0.21)	$p < 0.001$
cCRVE (μm) mean (SD)	1.46 (0.15)	1.82 (0.38)	$p < 0.001$
One year post-partum			
MAP (mmHG) mean (SD)	100.50 (15.22)	85.92 (7.89)	$p < 0.001$
cCRAE (μm) mean (SD)	1.11 (0.22)	1.35 (0.26)	$p < 0.001$
cCRVE (μm) mean (SD)	1.65 (0.36)	1.96 (0.30)	$p < 0.001$

[c]CRAE: corrected central retinal arteriolar equivalent; cCRVE: corrected central retinal venular equivalent; MAP: mean arterial blood pressure.

The mean cCRAE and cCRVE was significantly lower in the pre-eclamptic group compared with the control group both at delivery and one year. (Table 2) There was a 0.30 μm and 0.24 μm difference in cCRAE between the pre-eclamptic and control groups at delivery and one year respectively. The difference in cCRVE between the 2 groups at delivery was 0.36 μm and 0.31 μm at one year. There was a non-significant increase of 0.11 μm ($p = 0.10$) in the cCRAE between delivery and one year in the pre-eclamptic group. This correlated with a decrease in the MAP between the two time-periods (Figure 2(a) and (b)). The increase of 0.19 μm in the cCRVE in the pre-eclamptic group between delivery and one year was statistically significant ($p = 0.02$). A sub-analysis of the pre-eclamptic group was performed. The mean cCRAE for pre-eclamptic women at one year with chronic hypertension was 1.043 μm compared to 1.224 μm ($p = 0.0084$) for pre-eclamptic women who were normotensive. The mean cCRVE for pre-eclamptic women with chronic hypertension was 1.482 μm compared to 1.891 μm ($p = 0.0003$) for those who were normotensive. A receiver operator characteristic curve was used to determine whether cCRAE at delivery would predict hypertension at one year (MAP >110 mmHg). The area under the curve was 0.364 which was not significant. A cCRAE cut-off

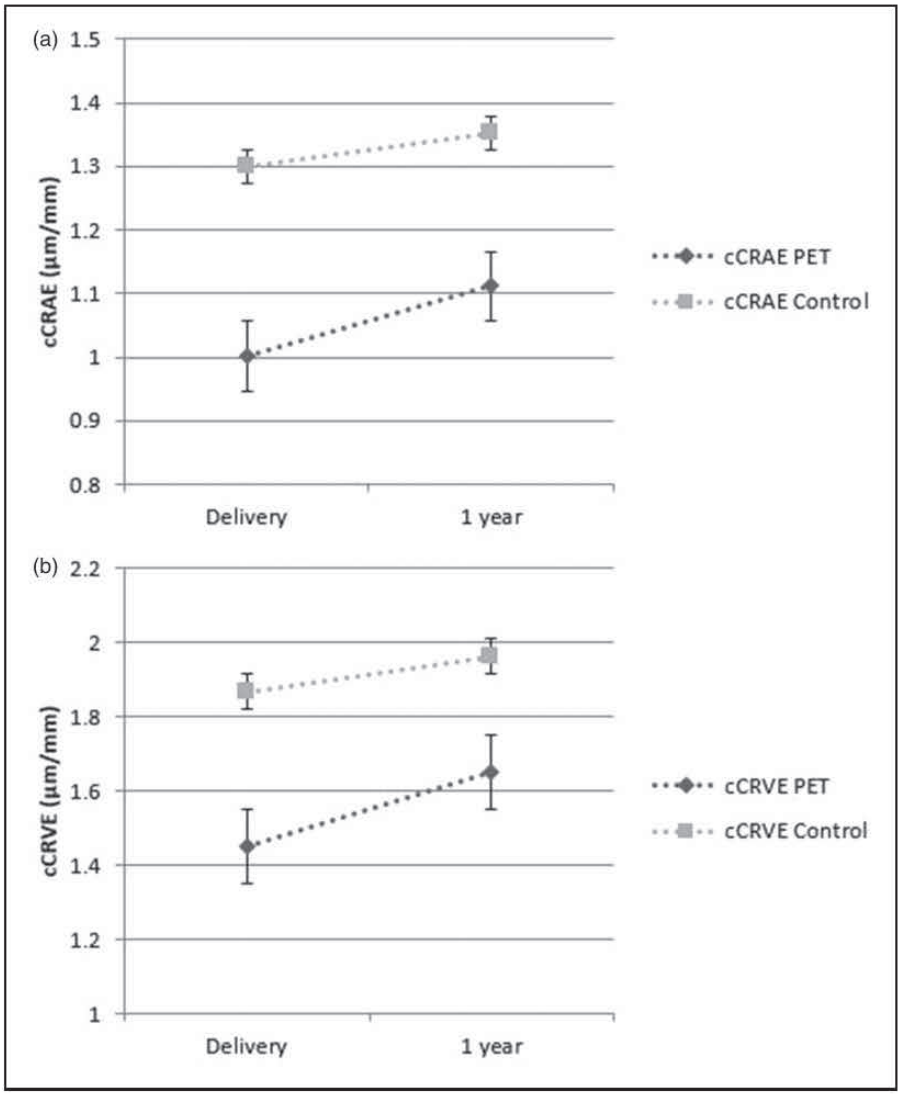

Figure 2. (a) Comparison of cCRAE between the pre-eclamptic group and control group (mean and standard deviation). (b) Comparison of cCRVE between the pre-eclamptic group and control group (mean and standard deviation) [AQ4].
cCRAE: corrected central retinal arteriolar equivalent; cCRVE: corrected central retinal venular equivalent.

Table 3. Comparison of cCRAE and cCRVE at one year between the women with pre-eclampsia and the different clinical sub-groups of women with pre-eclampsia.

	cCRAE (μm) at one year, mean (SD)	*p*-value	cCRVE	*p*-value
Pre-eclamptic group n = 40	1.11 (0.22)		1.65 (0.36)	
Early onset pre-eclampsia < 34 weeks n = 24	1.08 (0.23)	0.52	1.57 (0.39)	0.38
Pre-eclamptic women with diastolic dysfunction at one year n = 5	1.14 (0.29)	0.77	1.64 (0.41)	0.94
Pre-eclamptic women with WMLs at one year n = 17	1.15 (0.24)	0.59	1.74 (0.32)	0.41
Pre-eclamptic women with hypertension at one year n = 22	1.04 (0.17)	0.19	1.48 (0.29)	0.06

cCRAE: corrected central retinal arteriolar equivalent; cCRVE: corrected central retinal venular equivalent; WMLs: white matter lesions.

of 0.974937 μm has a sensitivity of 97.9% and a specificity of 34.7%. Therefore cCRAE at delivery is not a good predictor of hypertension at one year.

Sixty percent of women in the pre-eclamptic group developed early onset pre-eclampsia requiring delivery before 34 weeks. A sub-analysis of this pre-eclamptic group showed that these women had an increased risk of developing diastolic dysfunction one year after delivery. Table 3 compares the cCRAE and cCRVE of the pre-eclamptic group at one year to various clinical sub-groups within the group of women with pre-eclampsia. Although the cCRAE and cCRVE at one year were smaller in women with early onset pre-eclampsia requiring delivery < 34 weeks and for pre-eclamptic women with chronic hypertension at one year, these differences were not significant. These non-significant findings are possibly due to the small study numbers within the sub-group of pre-eclamptic women.

Discussion

Narrower retinal microvessel caliber seen in women with pre-eclampsia during pregnancy compared to a normotensive control group was first described by Lupton et al.[7,10] Ours is the first study to demonstrate that such retinal arteriolar and venular narrowing in women with pre-eclampsia during pregnancy persists for up to one year post-partum. Our study demonstrates longer-term effects of pre-eclampsia on the microvasculature and may provide insights into the higher risks of cardiovascular disease in women with a history of pre-eclampsia.

Retinal vascular changes are markers of early pathogenic processes in hypertension and are related to both subclinical and clinical end-organ damage. The association between arteriolar narrowing and development of later hypertension has been described by Ding et al.[31] As a precursor of hypertension, increased peripheral resistance (similar to conditions like pre-eclampsia) occurs primarily in small arteries and arterioles. Therefore, arteriolar narrowing may contribute to an elevation in blood pressure, eventually leading to hypertension and a 'vicious cycle' may develop in which the microcirculation maintains or even amplifies an initial increase in blood pressure.[21,22] This pattern is also evident in women who develop pre-eclampsia where arteriolar narrowing precedes the clinical onset of hypertension during pregnancy.[7] Retinal vessel caliber, during and after pregnancy, remains smaller in pre-eclamptic women than women who are normotensive during pregnancy and a proportion of women with pre-eclampsia during pregnancy will develop chronic hypertension. Fifty-five percent of women in our study remained hypertensive at one year. Pre-eclamptic women with chronic hypertension had significantly narrower retinal artery and venular calibers than pre-eclamptic women whose blood pressure normalised after delivery.

The strong, consistent association between pre-eclampsia and future cardiovascular disease was shown in a meta-analysis by Bellamy and colleagues.[13] Coronary and retinal vessels undergo similar changes (such as sclerosis) in patients with hypertension.[23] Assessment of retinal vessels has been shown to correlate with coronary microvascular damage.[23,24] It has been hypothesised that microvascular disease may play a greater role in the development of myocardial ischemia and definite coronary heart disease in women than in men.[25,26] Wong et al. found that retinal arteriolar narrowing is related to the risk of coronary heart disease in women but not in men.[27] In this study, every 1-SD decrease in the arteriole-to-venule ratio was associated with a 37% increase in coronary heart disease risk.

In a meta-analysis of 198,252 women with pregnancies affected by pre-eclampsia, the relative risk for the development of stroke after 10 years was 1.81, 95% CI 1.45–2.27.[13] Retinal arteriolar narrowing and decreasing arteriole-to-venule ratio have been shown to predict incident stroke as well as MRI-identified subclinical stroke.[11,12] The retinal and cerebral microvasculatures have been described as homologus.[28] Similar to changes in retinal vasculature, microvascular changes in the brain may lead to chronic ischemia and the development of WMLs. The disruption of the blood-brain barrier of the cerebral microcirculation is believed to be an important pathophysiological feature in the development of cognitive impairment and dementia.[29] Retinal vascular lesions are also believed to reflect a break-down of the blood-retinal barrier. Several studies have reported a relation between retinal vascular abnormalities and cognitive function.[30,31,32] In the hypertensive sub-group of the Cardiovascular Health Study, the presence of any retinopathy (OR 2.10, 95% CI 1.04–4.24) or focal arteriolar narrowing (OR 3.2, 95% CI 1.51–6.02) was associated with an increased risk of dementia.[31]

The strength of this study is that this is the first study to show that retinal vessel narrowing associated with pre-eclampsia persists in the post-partum period. The study is limited in that retinal vessel caliber was analysed in only a select group of patients from the larger study evaluating cardiac diastolic function and cerebral WMLs after pre-eclampsia, and there were no pre-pregnancy readings of retinal vessel calibre. The smaller numbers means that a possible association between retinal vessel calibre, cerebral WMLs and diastolic dysfunction could not be determined accurately.

Conclusion

Retinal arteriolar and venular calibre changes that occur during pregnancies affected by pre-eclampsia persist for up to one year post-partum. These changes may be a reflection of permanent, long-term microvascular dysfunction in other organs systems and have been shown to be a predictor of future cardiovascular risk. Pre-eclampsia has a long-term negative effect on maternal health and strategies to prevent the development of pre-eclampsia should be explored further.

Declaration of conflicting interests

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Ethical approval

Ethical approval was obtained from the University of Pretoria Research Ethics Committee (No. 125/2013). [AQ2]

Guarantor [AQ3]

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Contributorship

PSP, RP, TYW and RCP designed the study and wrote the manuscript. PSP took the fundus photographs and TYW was responsible for grading of fundus photos. JDM carried out the statistical analyses.

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CLINICAL ARTICLE

Quality of life 1 year after a maternal near-miss event

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Keywords: Future fertility; Hypertension; Live birth rate; Maternal near-miss; Medical condition in pregnancy; Perinatal loss; Quality of life.

Synopsis: Women categorized with a maternal near-miss during pregnancy reported worse quality of life at 1 year after delivery than did women who experienced uncomplicated pregnancies.

ABSTRACT

Objectives: To evaluate quality of life (QoL) parameters among women categorized with a maternal near-miss during pregnancy.

Methods: The present prospective cohort study was conducted at a tertiary referral hospital in South Africa between April 1, 2013, and March 31, 2016. Patients who experienced maternal near-miss events were included and patients with uncomplicated low-risk pregnancies were enrolled as a control group. Various parameters were assessed using a WHO QoL questionnaire.

Results: The maternal near-miss and uncomplicated low-risk pregnancy (control) groups comprised 95 and 51 women. The maternal near-miss group scored lower than the control group in all four domains of the questionnaire (P<0.001). Overall, 42 (82%) women in the control group and 41 (43%) women in the maternal near-miss group desired future fertility (P<0.001). Women in the maternal near-miss group who had experienced perinatal loss scored lower in the physical health and well-being (P=0.009), psychological health and well-being (P=0.007), and environment (P=0.031) domains compared with women in the maternal near-miss group who experienced a live delivery. Nonetheless, QoL scores among women in the maternal near-miss group who had experienced perinatal loss remained lower than those reported by women in the control group (P< 0.001).

Conclusion: A maternal near-miss event during pregnancy was associated with reduced QoL, especially among women who had experienced perinatal loss.

1 INTRODUCTION

Maternal near-miss is defined as the survival of a potentially life-threatening obstetric complication during pregnancy [1]. Women often experience immediate and long-term physical, social, financial, and psychological consequences after a maternal near-miss event [2]. Indeed, Filippi et al. [3] found that women categorized with maternal near-miss remained at increased risk of mortality and experienced poor mental-health outcomes (e.g. suicidal ideation and depression) during the first 3 months after delivery.

Quality of life (QoL) has been defined by WHO [4] as, “an individual’s perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns”. The consequences of maternal near miss on post-delivery QoL is uncertain

The aim of the present study was to examine QOL among women who had been categorized with maternal near miss in comparison with women who had experienced an uncomplicated low-risk pregnancy.

2 METHODS

The present prospective cohort study conducted at Steve Biko Academic Hospital (SBAH) in Pretoria, South Africa. Patients were recruited between April 1, 2013, and March 31, 2015, with 1-year follow-up visits scheduled between April 1, 2014, and March 31, 2016. Patients who experienced maternal near-miss events were eligible for inclusion and a control group was recruited from patients who had uncomplicated

low-risk pregnancies. Approval for the present study was obtained from the Research Ethics Committee of the University of Pretoria, South Africa. The participants were informed of the purpose of the present study and told that their responses would remain confidential. Informed consent was subsequently provided by all women included in the analysis.

Approximately 10% of all deliveries that occur at SBAH, a tertiary referral hospital, are considered to have a low level of exposure to danger, mainly as the result of low-risk women presenting in labor for the first time. Low-risk patients were identified by completing the Guidelines for Maternity Care in South Africa [5] checklist, a basic prenatal care approach used in all South African public institutions. The present study formed part of a larger study comparing cardiac function between women with pre-eclampsia and those at low risk of this complication. The cardiology department at SBAH reserved echocardiographic appointments every Wednesday for low-risk women. The first such patient who experienced a low-risk delivery each Wednesday (as recorded in the maternity register) was subsequently recruited to the control group.

Maternal near-miss cases were prospectively identified at daily audit meetings held at SBAH using the criteria defined by WHO (Box 1) [6]..

Both groups of women attended a postnatal visit at 1 week after delivery. Women in the maternal near-miss group also attended the SBAH maternal near-miss clinic on a monthly basis after delivery if they required chronic administration of medication.

All participants received a 1-year follow-up visit to assess post-delivery QoL. A questionnaire designed by WHO (WHOQOL-BREF) [4] was completed during personal interviews conducted by female interviewers experienced in the local dialect (should the participants be illiterate or unable to speak English). The WHOQOL-BREF questionnaire contains two items assessing overall QoL and general health; seven items assessing physical health; six items assessing psychological health; three items assessing social relationships; and eight items assessing environmental health. Each item is rated on a five-point scale, with a score of 1 reflecting poor QoL and a score of 5 reflecting very good QoL. The WHO-QoL questionnaire is further grouped in four domains that assess physical health and well-being (domain 1), psychological health and well-being (domain 2), social relations (domain 3), and the environment (domain 3). The participants were also asked about their desire for future fertility.

The data were analyzed using SPSS version 24.0 (IBM, Armonk, NY, USA). The descriptive analyses included frequencies and percentages for categorical data, with ranges, means, and standard deviations for continuous data. Linear regression analysis was used to assess which specific conditions underlying the maternal near-miss event (hypertension; hemorrhage; medical disorders in pregnancy; infection not related to pregnancy; or pregnancy-related infection) were independent predictors of the WHOQOL-BREF score. The reliability of WHOQOL-BBREF questionnaire was assessed using the Cronbach α, with a score of at least 0.70 deemed to be acceptable [7]. A *P* value of less than 0.05 was considered statistically significant.

3 RESULTS

A total of 6536 deliveries were recorded at SBAH during the recruitment phase. There were 133 maternal near-miss events, of which 18 (13.5%) resulted in death. The obstetric causes underlying maternal near-miss are described in Table 1. The most frequently recorded causes were obstetric hemorrhage and hypertension. The mortality index was 2.0% and 13.6% for hemorrhage and hypertension, respectively. In total, 110 of the 133 women who had experienced maternal near-miss and 55 patients with uncomplicated low-risk pregnancy were recruited to the present study. There were 15 patients with a maternal near-miss event and four with an uncomplicated low-risk pregnancy who were lost to follow-up and were excluded from the analyses. Consequently, the maternal near-miss and control groups comprised 95 and 51 women, respectively, all of whom completed the WHOQOL-BREF questionnaire.

The characteristics of the two groups are shown in Table 2. A statistically significant between-group difference was found for live delivery rate only (P<0.001). The majority of stillbirths occurred in women with abruption placentae and most of these women presented with fetuses who had demised in utero. In the control group, 1 (2%) patient presented at term with loss of fetal movements and intrauterine fetal demise; a macerated stillborn was delivered vaginally.

Table 3 outlines responses to each item included in the WHOQOL-BREF questionnaire. The control group scored significantly higher than the maternal near-miss group for all QoL measures assessed (P<0.001), with the exception of body image (P=0.521). The highest mean score for the maternal near-miss group was for

pain (4.27; indicating that daily life was not affected), whereas the highest mean score for the control group was for dependence on medical aids (4.94; indicating that medical treatment was not needed to function normally). The lowest mean score recorded for both groups was for lack of financial security (2.62 for the maternal near-miss group and 3.31 for the control group).

The items included in the WHOQOL-BREF questionnaire were grouped into four domains that evaluated physical health and well-being; psychological health and well-being; social relations; and environment (Table 4). Women in the maternal near-miss group scored lower for each of these domains when compared to women in the control group (P<0.001). The reliability of the WHOQOL-BREF questionnaire was found to be adequate (Cronbach α coefficient, 0.964).

In all, 42 (82%) women in the control group and 41 (43%) women in the maternal near-miss group expressed a desire for additional children (P<0.001). Conversely, 6 (12%) women in the control group and 7 (7%) women in the maternal near-miss group were uncertain about their desire for future fertility. Women in the maternal near-miss group scored the lowest when questioned about their financial status. This discrepancy was highlighted in the participants' narratives, with many references to loss of income either because of separation from a partner or loss of employment:

"The pregnancy caused a set-back in my life. I was forced to leave my job. Now I have money problems. My mother has to look after my 5-year old." [Maternal near-miss participant number 32, interview on social relations]

"I lost my job while in the hospital. I cannot get another job because I am too weak. I am getting a grant." [Maternal near-miss participant number 2, interview on physical health and well-being]

"My boyfriend broke-up with me because I lost the baby." [Maternal near-miss participant number 24, interview on social relations]

"I have marriage problems and I am very stressed." [Maternal near-miss participant number 83, interview on social relations]

Certain QoL variables were also assessed within the maternal near-miss group. Women in receipt of a social grant scored lower for the following items than did women who were not dependent on social support: pain (P=0.024); dependence on medical aids (P=0.026); body image (P=0.014); mobility (P=0.025); and negative feeling (P=0.033). By contrast, no statistically significant differences were found for any components of the WHOQOL-BREF questionnaire (including the four domain scores) among women infected with HIV versus those who were not infected with HIV.

Women in the maternal near-miss group who had been discharged from SBAH after experiencing perinatal loss scored lower for the following components than did women in the maternal near-miss group whose pregnancy had resulted in a live birth: overall health (P=0.004); positive feeling (P=0.002); personal belief (P=0.001); concentration (P=0.027); security (P=0.031); energy (P=0.004); leisure activity (P=0.013); self-esteem (P=0.029); and home environment (P=0.033). Women who

had experienced both maternal near-miss and perinatal loss also scored lower than their counterparts with a live birth in the following three domains: physical health and well-being (*P*=0.009); psychological health and well-being (*P*=0.007); and environment (*P*=0.031). No difference was found between these two groups with regard to social relations (*P*=0.119).

A sub-analysis was performed to evaluate QoL among all of the women who were discharged from hospital following a live delivery. When compared with the control group, women in the maternal near-miss group scored lower for all components and domains of the WHOQOL-BREF questionnaire (*P*<0.001), with the exception of security (*P*=0.084), body image (*P*=0.977), and sexual activity (*P*=0.159).

The underlying obstetric causes among the 95 women included in the maternal near-miss group were hypertension (37 [39%]); obstetric hemorrhage (34 [36%]); medical condition during pregnancy (20 [21%]); infection not related to pregnancy (2 [2%]); and pregnancy-related infection (2 [2%]). Patients who experienced maternal near-miss events linked to a medical condition in pregnancy scored lower for energy compared with patients who had near-miss events related to hemorrhage, hypertension and infection (95% confidence interval [CI] –1.02 to –0.082; *P*=0.022), body image (95% CI –0.958 to –0.082; *P*=0.021), mobility (95% CI –1.140 to –0.086; *P*=0.023), physical health and well-being (95% CI –4.375 to –0.436; *P*=0.017), and psychological health and well-being (95% CI –3.849 to –0.436; *P*=0.014). No statistically significant differences in QoL scores were found when patients were stratified by maternal near-miss events due to hypertension, hemorrhage, infection unrelated to pregnancy, or pregnancy-related infection.

4 DISCUSSION

The present study provided important information for understanding how maternal near-miss events can affect QoL among women after delivery. Of note, women in the maternal near-miss group scored substantially lower than women in the control group on all domains of the WHOQOL-BREF questionnaire at the 1-year follow-up visit.

The live birth rate in the present study was lower in the maternal near-miss group than in the control group (64% vs 98%). Interestingly, women in the maternal near-miss group who had experienced perinatal loss scored markedly lower on nine components and three domains of the WHOQOL-BREF questionnaire than did women in the maternal near-miss group who had experienced a live birth. A quantitative analysis of postpartum psychological function found that perinatal loss was important for initiating symptoms of psychological distress [8]. Unfortunately these adverse pregnancy events result in mothers carrying the long-term burden of an overall QoL that is poorer than that of women who have had uncomplicated pregnancies; the effects of a poorer QoL are often carried over into subsequent pregnancies [9].

Both study groups had insufficient money for daily needs but the deficit was a greater problem for women in the near-miss group who recorded the lowest scores for financial security. This finding reflected either loss of income because women were unable to continue working in jobs that they had previously occupied or else the fact that the maternal near-miss event had resulted in separation from their partners,

on whom they were previously dependent for financial support. In some cases, lack of money led to a breakdown of the family unit, with children being cared for by other family members who did not live in the same household. As a result of job loss, some women in the maternal near-miss group became dependent on social support grants, which in turn was associated with low scores for some components of the WHOQOL-BREF questionnaire. The words “diversity” and “divergence” have been used to describe the cycle of poor maternal health [10]. Diversity refers to the degree and causes of maternal health problems; divergence describes the disparity in maternal mortality between women living in high-income countries and vulnerable populations such as in Sub-Saharan Africa. Women in lower- and middle-income countries are considered vulnerable because of where they live and who they are [10]. Such women carry the risk of increased maternal morbidity, which progresses to low QoL aggravated by poor social and economic burden. The women who experienced a maternal near-miss in the present study fall into this category.

The current scores recorded for personal relationships in the maternal near-miss and control groups suggested that such relationships were potentially strained among the women who had experienced a maternal near-miss event. Traumatic birth events have been found to provoke intense anxiety and fear among male partners, resulting in long-term consequences for both them and their families [11]. Other studies have found that men can experience various feelings after an obstetric emergency, including alienation, lack of empowerment, information deprivation, and exclusion from their partners [12–15]. Some men also become withdrawn from their social networks and might be reluctant to seek support as such behavior is believed to contradict societal expectations [11].

Although both the maternal near-miss and control groups exhibited similar age and parity, the present study found that fewer than half of all women who had experienced a maternal near-miss event expressed a desire for future children. This high loss of reproductive potential probably reflects the severity of the adverse event, as well as the subsequent physical and emotional consequences [16].

Several studies have reported that mothers infected with HIV experience more morbidity and mortality during the first 2 years after delivery than do women who are not infected with HIV [17–19]. The present study found that HIV status was not associated with a statistically significant difference in QoL at 1 year after delivery among women in the maternal near-miss group. No statistically significant differences in QoL were found for other obstetric causes of maternal near-miss, other than for an underlying medical disorder in pregnancy.

To the best of our knowledge, the present study was the first conducted in South Africa to compare QoL among women who had experienced maternal near-miss events with that of women who had experienced uncomplicated low-risk pregnancies. However, the present study was limited in that only a portion of all maternal near-miss patients were interviewed. Furthermore, all women categorized with a maternal near-miss event in the present study had access to targeted healthcare in the form of a maternal near-miss clinic. This clinic was particularly beneficial for women with chronic hypertension and other chronic medical conditions because a single clinic could meet all of their medical needs. Medical personnel at the maternal near-miss clinic consulted other specialist disciplines if needed. In

addition, women who attended the clinic were able to develop a support system with other mothers who had similar experiences. Therefore, the present results cannot be generalized to the South African population as SBAH hosts the only known maternal near-miss clinic in the country. Women who do not have access to such a clinic might record even lower scores on QOL questionnaires.

In conclusion, measures of QoL might be reduced among women who have experienced maternal near-miss, a situation that is aggravated by perinatal loss. Institutions are therefore recommended to establish a database of maternal near-miss events as part of their prenatal and postnatal maternal-health programs.

Author contributions

PSP and RCP designed the study and wrote the manuscript. JDM analyzed and interpreted the data, conducted the statistical analyses, and wrote the manuscript.

Conflicts of interest

The authors have no conflicts of interest.

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Box 1 The maternal near-miss criteria defined by WHO [6].

Clinical

- Acute cyanosis
- Oliguria unresponsive to fluids or diuretics
- Jaundice concomitant with pre-eclampsia
- Shock
- Cerebrovascular accident
- Breathing rate >40/min or <6/min
- Loss of consciousness, with no pulse and/or heartbeat
- Gasping
- Coagulation disorders
- Total paralysis

Laboratory

- Oxygen saturation <90% for >1 h
- Serum creatinine level >300 μmol/L (>3.5mg/dL)
- Unconscious, with glucose and ketoacidosis detected in the urine
- Ratio of PaO_2 to FiO_2 <200 mm Hg
- Acute thrombocytopenia (<50 000 platelets)
- Serum bilirubin level >100 μmol/L (>6.0 mg/dL)
- Plasma lactate level >5mg/dL
- pH <7.1

Management

- Use of vasoactive drug (intravenous)
- Puerperal hysterectomy owing to infection or hemorrhage
- Transfusion with >5 units of red blood cell concentrate
- Dialysis for treatment of acute kidney failure
- Cardiopulmonary resuscitation
- Intubation and ventilation for a period of >1 hour, unrelated to anesthesia

Abbreviations: FiO_2, fraction of inspired oxygen; PaO_2, partial pressure of oxygen in the arterial blood.

Table 1 Primary obstetric cause for the maternal near-misses (n=95). [a]

Cause	No. (%)
Medical condition	14 (15)
Infection unrelated to pregnancy	3 (3)
Spontaneous abortion	7 (7)
Pregnancy-related infection	3 (3)
Obstetric hemorrhage	37 (39)
Hypertension	28 (29)
Anesthetic complications	2 (2)
Acute collapse of unknown cause	1 (1)

[a] Values are given as number (percentage).

Table 2 Demographic characteristics of the participants. [a]

Characteristic	Maternal near-miss group (n=95)	Control group (n=51)
Age, y [b]	28.3 ± 6.83 (18–46)	27.4 ± 7.14 (20–42)
Ethnicity		
African	85 (90)	42 (82)
White	5 (5.)	4 (8)
Black (not of African origin)	4 (4.)	5 (10)
Indian	1 (1)	0 (0)
Parity [c]	1.3 (0–4)	1.6 (0–5)
Timing of delivery, wk		
<34	44 (46)	0 (0)
34–37	25 (26)	5 (10)
>37	26 (27)	46 (90)
Live delivery rate [d]	61 (64)	50 (98)
Tubal ligation or hysterectomy performed during pregnancy		
Yes	11 (12)	2 (4)
No	84 (88)	49 (96)

[a] Values are given as mean±SD (range), number (percentage), or mean (range).
[b] Independent-sample *t* test; *P*=0.663.
[c] Independent-sample *t* test; *P*=0.712.
[d] Independent-sample *t* test; *P*<0.001.

Table 3 Responses for each item included in the WHO quality-of-life questionnaire [4]. [a, b]

Item	Maternal near-miss group (n=95)			Control group (n=51)		
	Score	Scored at lowest level	Scored at highest level	Score	Scored at lowest level	Scored at highest level
Overall quality of life	3.56 ± 0.9	2 (2)	13(14)	4.47 ± 0.6	2 (4)	25 (49)
Overall health	3.67 ± 1.0	1 (1)	19 (20)	4.65± 0.5	17 (33)	30 (59)
Pain preventing daily work [c]	4.27 ± 0.9	4 (4.)	50 (53)	4.91 ± 0.3	4 (8)	45 (88)
Dependence on medical aids for daily function [c]	4.00 ± 0.9	1 (1)	29 (31)	4.94 ± 0.2	2 (4)	48 (94)
Positive feeling	3.52 ± 0.9	3 (3.)	9 (10)	4.25 ± 0.7	6 (12)	19 (37)
Personal belief	3.46 ± 0.8	1 (1)	5 (5)	4.20 ± 0.7	10 (20)	20 (39)
Concentration	3.74 ± 0.7	2 (2)	7 (7)	4.61 ± 0.5	1 (2)	31(61)
Security	3.55 ± 0.9	1 (1.)	9 (10)	3.96 ± 0.8	18 (35)	17(33)
Physical environment	3.43 ± 0.9	1 (1)	7 (7	4.08 ± 0.8	15(29)	19 (37)
Energy	3.80 ± 0.8	1 (1)	17 (18)	4.33 ± 0.5	1 (2)	17 (33)
Body image	3.71 ± 0.8	6 (6.)	14 (15)	3.80 ± 0.7	18 (35)	8 (16)
Financial security	2.62 ± 0.9	7 (7.	3 (3)	3.31 ± 0.7	3 (6)	1 (2.)
Accessibility of information	2.98 ± 0.9	29 (31)	5 (5.)	4.02 ± 0.6	1 (2)	8 (16)
Leisure activity	2.87 ± 0.9	5 (5.)	4 (4.)	4.16 ± 0.6	1 (2.)	14 (28)
Mobility	3.18 ± 1.0	1 (1)	8 (8)	4.12 ± 0.6	6 (12)	12 (24)
Sleep and rest	3.80 ± 0.9	11 (12)	20 (2)	4.63 ± 0.5	1 (2)	31 (61)
Activities of daily living	3.87 ± 0.8	5 (5.)	16 (17)	4.69 ± 0.5	16 (31)	34 (67)
Work capacity	3.88 ± 0.8	7 (7.	17 (18)	4.67 ± 0.6	3 (6)	36 (71)
Self-esteem	3.80 ± 0.8	7 (7.	16 (17)	4.56 ± 0.5	22 (43)	28 (55)
Personal relationship	3.71 ± 0.9	1 (1.)	18 (19)	4.27 ± 0.7	6 (12)	19 (37)
Sexual activity	3.78 ± 0.9	2 (2.)	21 (22)	4.08 ± 0.7	12 (24)	15 (29)
Social support	3.49 ± 0.9	1 (1.)	9 (10)	4.31 ± 0.6	5 (10)	18 (35)
Home environment	3.52 ± 0.9	1 (1)	13 (14)	4.14 ± 0.7	9 (18)	16 (3)
Health care	3.74 ± 0.9	10 (11)	17 (18)	4.45 ± 0.6	4 (8)	25 (49)
Transport	3.26 ± 0.9	20 (21)	9 (10)	4.21 ± 0.6	5 (10)	15 (29)
Negative feeling	3.73 ± 0.9	9 (10)	16 (17)	4.51 ± 0.6	1 (2)	28 (55)

[a] Values are given as mean±SD or number (percentage).
[b] Independent-sample *t* test; *P*<0.001 for all comparisons, other than body image (*P*=0.521).
[c] Scores ranged from 1 (an extreme amount) to 5 (not at all).

Table 4 Comparison of the four domain scores. [a, b]

Domain	Maternal near-miss group	Control group
Physical health and well-being	26.8 ± 4.2	32.3 ± 2.3
Psychological health and well-being	21.9 ± 3.6	26.0 ± 2.7
Social relations	11.0 ± 2.3	12.7 ± 1.9
Environment	26.0 ± 5.4	32.5 ± 3.9

[a] Values are given as mean±SD.
[b] Independent-sample *t* test; *P*<0.001 for all comparisons.