Liste des abréviations

AC	Assisted conception
ASQ	Ages and Stages Questionnaire
GA	Gestational Age
ICSI	Intra Cytoplasmic Sperm Injection
IVF	In Vitro Fertilization
LBW	Low Birth Weight
LIFT	Loire Infant Follow-up Team
SD	Standard Deviation
SGA	Small for Gestational Age

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ABSTRACT

Introduction: Assisted conception (AC) appears to increase the rate of premature births, though few studies have analysed outcomes for these preterm infants. The aim of this study was to evaluate the effect of AC on neonatal morbidity and mortality and on neurodevelopmental outcome at 2-years in preterm infants born before 34 weeks of gestational age (GA).

Methods: All infants born alive between 24^{+0} and 33^{+6} weeks GA and hospitalised at the Angers University Hospital between January 2009 and December 2013 were eligible as long as the mode of conception was known. Live infants at discharge were enrolled in the Loire Infant Follow-up Team (LIFT) prospective longitudinal cohort. Neonatal morbidity and mortality were evaluated during hospitalisation based on a composite score including death, intraventricular haemorrhage grade ≥3, periventricular leukomalacia, treated patent ductus arteriosus and bronchopulmonary dysplasia at 36 weeks GA. The neurodevelopmental outcome at 2-years of corrected age was appreciated by a physical examination, a neuropsychological test and a parental questionnaire. Infants were matched 1:1 according to maternal age, twin status and propensity score.

Results: 703 preterm infants were included in the analysis of neonatal morbidity and mortality, including 137 born after AC. There was no significant association between AC and neonatal morbidity and mortality (aOR 0.67, 95% CI [0.25, 1.77], p=0.422). 573 infants were assessed at 2 years, including 121 born after AC. AC was significantly associated with a reduction in the probability of non-optimal neurological development at 2 years (aOR 0.26, 95% CI [0.09, 0.80], p=0.019).

Conclusion: AC was not associated with an increase in neonatal morbidity and mortality and was even significantly associated with a better 2-year neurodevelopmental outcome in preterm infants born before 34 weeks GA. Further studies remain necessary to fully confirm these results.

Keywords: assisted conception, prematurity, neonatal morbidity and mortality, neurodevelopment

ARTICLE

1. Background

Since the start of in vitro fertilization (IVF) and the birth of Louise Brown in 1978, 6.5 million infants have been born by IVF worldwide [1]. In France, INSEE (French national statistics office) counted 25,208 infants born after assisted conception (AC) in 2014, i.e. 3.1% of all births in 2014.

Some AC-related effects are now known and supported by extensive publications, including several meta-analyses: independently of the increase in twin status, AC would appear to increase the risk of preterm and very preterm birth, low birth weight (LBW), along with the risk of infants born small for gestational age (SGA) [2-8]. According to the large cohort study by Ombelet et al. [8], births of preterm singletons increase significantly in cases of IVF conception, with or without intracytoplasmic sperm injection (ICSI) (OR 1.92, 95% CI [1.79, 2.05]) and after conception following ovarian stimulation alone (OR 1.31, 95% CI [1.23, 1.40]) by comparison to spontaneously conceived singletons. Moreover, several studies have reported an increase in the risk of birth defects following IVF conception [9-13] (aRR 1.28, 95% CI [1.15, 1.42]) according to the study by Boulet et al. [13] on an American cohort of 4,618,076 infants, including 64,861 IVF.

Animal studies highlight the possible change of epigenetic markers following ovarian stimulation, along with the handling, freezing and thawing of gametes and embryos [14] added to a number of potential indirect effects by propagation of abnormal epigenetic markers underpinned by infertility. Indeed the study by Seggers et al. in 2016 revealed, through an "intersibling" approach, an association between the characteristics of subfertile mothers and both lower birth weight and shorter gestational period [15].

The neurodevelopmental outcome in infants born after AC has also been studied [16-18]. The study by Ponjaert-Kristoffersen et al. [17] failed to show any differences in cognitive or motor development at 5 years. It should be noted, however, that Strömberg et al. observed an increase in cerebral palsy in singletons conceived by IVF, including after adjustment for gestational age and birth weight (OR 2.8, 95% CI [1.3, 5.8])[18].

Only five studies (of which 3 retrospective) analysed neonatal morbidity and mortality in preterm infants born after AC, though they failed to show any differences in survival without major morbidity [19-23]. Only one study analysed the neurodevelopmental outcome in preterm infants born after AC [24], but this study focused on extremely premature infants (born before 29 weeks of gestational age (GA)).

The aim of this study was to evaluate the impact of mode of conception on neonatal morbidity and mortality and on neurodevelopmental outcome at 2 years of corrected age in preterm infants born before 34 weeks GA.

2. Methods

2.1. Study population

This is a prospective monocentric study. All infants born alive between 24^{+0} and 33^{+6} weeks GA, between 1 January 2009 and 31 December 2013 and hospitalised in the Neonatal Intensive Care Unit of the Angers University Hospital were eligible as long as the mode of conception was known. Infants born before 34 weeks GA and alive at discharge were enrolled in the Loire Infant Follow-up Team (LIFT) follow-up programme. Infants with polymalformative or genetic syndrome were excluded. Infants whose parents had declined their participation in the Loire Infant Follow-up Team (LIFT) follow-up programme were also excluded.

Clinical data (obstetrical and neonatal) were collected prospectively for all preterm infants enrolled in the LIFT network. The clinical data for infants deceased during hospitalisation were collected retrospectively from their medical records. Birth weights were expressed in relation to GA as z-scores for standard deviations (SD) from Olsen growth curves [25].

The following pregnancy-related maternal data were collected retrospectively from the medical records for all infants: mode of conception and technique used if AC (ovarian stimulation, intrauterine insemination, in vitro fertilization (IVF) with or without ICSI (Intra-Cytoplasmic Sperm Injection)), maternal Body Mass Index (BMI) at onset of pregnancy, socio-economic status (INSEE classification),

universal health coverage (CMU - Couverture Médicale Universelle), smoking before and during pregnancy.

2.2. Primary outcome

The primary outcome was neonatal morbidity and mortality at discharge. We used a composite score including: death, grade 3 and/or 4 intraventricular haemorrhage, periventricular leukomalacia, medically and/or surgically treated patent ductus arteriosus and bronchopulmonary dysplasia (defined as oxygen requirement at 36 weeks of corrected GA).

2.3. Secondary outcome

The secondary outcome was non-optimal neurodevelopment at two years of corrected age. The neurodevelopmental assessment included a physical examination by a trained paediatrician and a psychomotor evaluation by a LIFT network psychologist. Neuromotor function was regarded as non-optimal when cerebral palsy was present or when the clinical examination revealed neurological signs of abnormal muscle tone (phasic stretch in the triceps surae muscle and imbalance passive axial tone with predominance of extensor tone) during independent walking. The psychomotor assessment was performed using the revised Brunet-Lézine test. This test covers four domains (movement and posture, language, socialisation, and coordination) and allows calculation of four sub-scores that, when combined, yield a global developmental score. The mean and maximum global developmental scores were 100 and 140, respectively, and values < 85 were considered to reflect non-optimal psychomotor development. Infants who were not able to perform the Brunet-Lézine test because of severe neurologic impairment were considered to have non-optimal psychomotor development. When a psychological evaluation was not performed, psychomotor function was assessed using the parental Ages and Stages Questionnaire (ASQ). The maximum overall ASQ score was 300. According to a previous study, we defined an overall ASQ score of < 185 as non-optimal [26]. Infants with non-optimal neuromotor and/or psychomotor assessments were regarded as having an overall "non-optimal neurodevelopmental outcome".

2.4. Statistical analysis

To ensure comparability between infants who were conceived by AC and those who were spontaneously conceived, these two populations were matched. Indeed, these differences could lead to major bias because of the known characteristics of mothers that need fertility treatment. For both analyses, risk of neonatal mortality/morbidity and risk of non-optimal neurodevelopment at two years of age, infants were matched on propensity scores with a 0.2 standard deviation caliper and with a ratio 1:1. Moreover, the matching procedures were exact regarding the mother's age (considered as a 4-class categorical variable: 16-24, 25-30, 31-35 and 36-48 years old) and the twin status (yes versus no). The propensity scores, corresponding to the probabilities for an infant to be born after assisted conception, were calculated with the following variables: gestational age (32-34, 28-31 and 24-27 weeks GA), z-score of birth weight (<-1, -1 to 0, 0 to 1 and >+1 standard deviation SD), antenatal treatments (corticosteroids and magnesium sulphate), gender, parity (1, 2 and 3 or more), Body Mass Index of the mother (15-18.4, 18.5-24.9 and 25-57 kg/m²), tobacco consumption of the mother during pregnancy (yes versus no), outborn delivery (yes versus no) and the socio-economic status of the mother (intermediate versus high). The balances after matching were checked between the two populations, both visually using propensity scores boxplots, and quantitatively using standardized differences.

The possible effects of assisted conception on the risk of neonatal mortality/morbidity and on the risk of non-optimal neurodevelopment at two years of age were quantified using a generalised estimation equation model to account for the matching between infants. All the variables used to calculate the propensity scores were used as adjustment variables in the final model as small differences could persist between the two populations of infants after matching. All of the statistical analyses were performed using R software.

2.5. Ethical statements

Written informed consent was obtained from the parents before the infants were included in the LIFT cohort and before gathering the relevant neonatal data from the clinical records. The cohort was registered at the French CNIL (Commission Nationale de l'Informatique et des Libertés no. 851117, ethics committee for the collection of the clinical data from the patient records). Specific approval to use the data in this study was obtained from the Ethics Committee of Angers.

3. Results

3.1. Study population

Between January 2009 and December 2013, 836 liveborn infants delivered before 34 weeks GA were hospitalised in the Angers University Hospital Neonatal Intensive Care Unit. Among these infants, 68 had not been included in the LIFT cohort due to parental refusal, or to parental domiciliation outside of the Pays de la Loire Region. Next, of the 768 infants included in LIFT, 25 presenting with a malformative syndrome were excluded, along with 40 infants for whom data were missing. The analysis of neonatal morbidity and mortality thus involved 703 infants. 37 infants died before discharge and 93 were lost of follow-up before their second year (secondary refusal or moved away from the Pays de la Loire Region). The analysis of 2-year neurodevelopment thus involved 573 infants (Figure 1). In order to ensure optimum comparability between infants born after AC and those conceived spontaneously, the infants were matched: Figures 2 and 3 show population comparability before and after matching according to propensity score (Figure 2) and Standardized Differences (Figure 3).

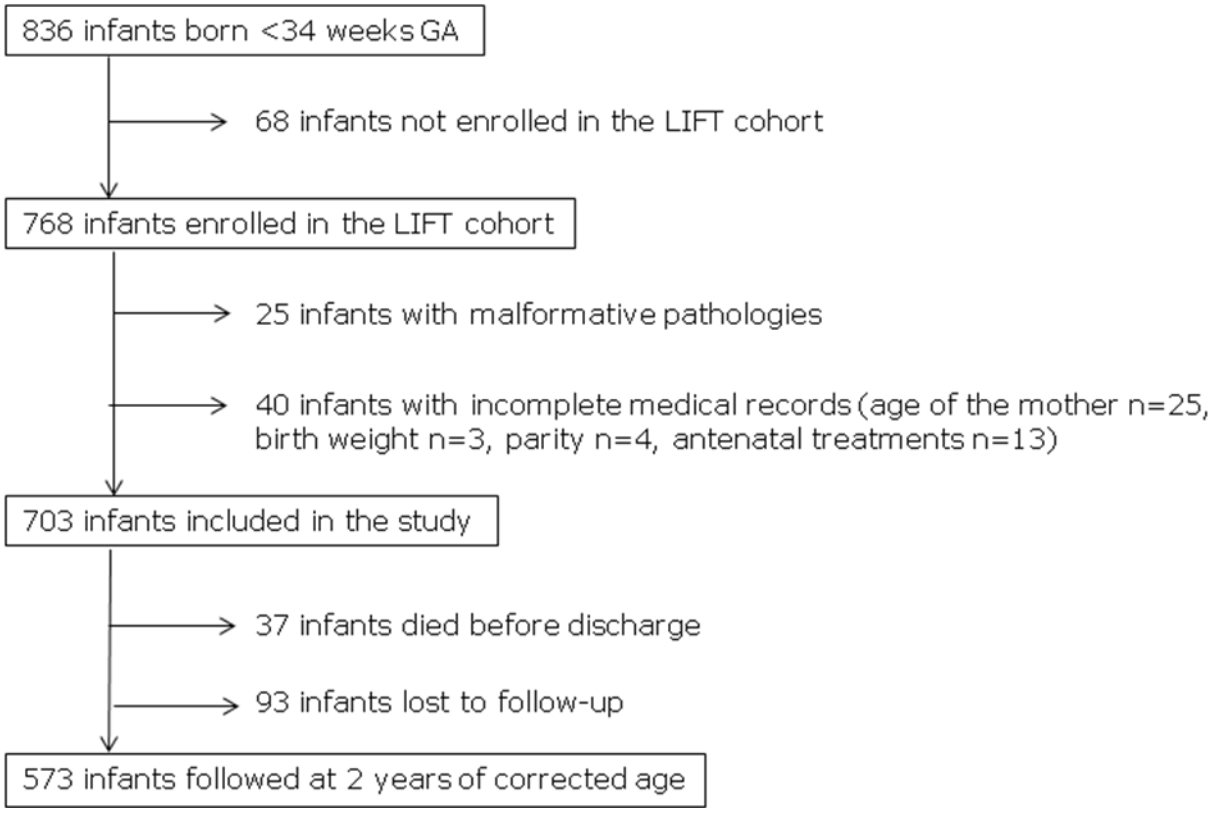

Figure 1. Flowchart.

GA: Gestational Age, LIFT: Loire Infant Follow-up Team

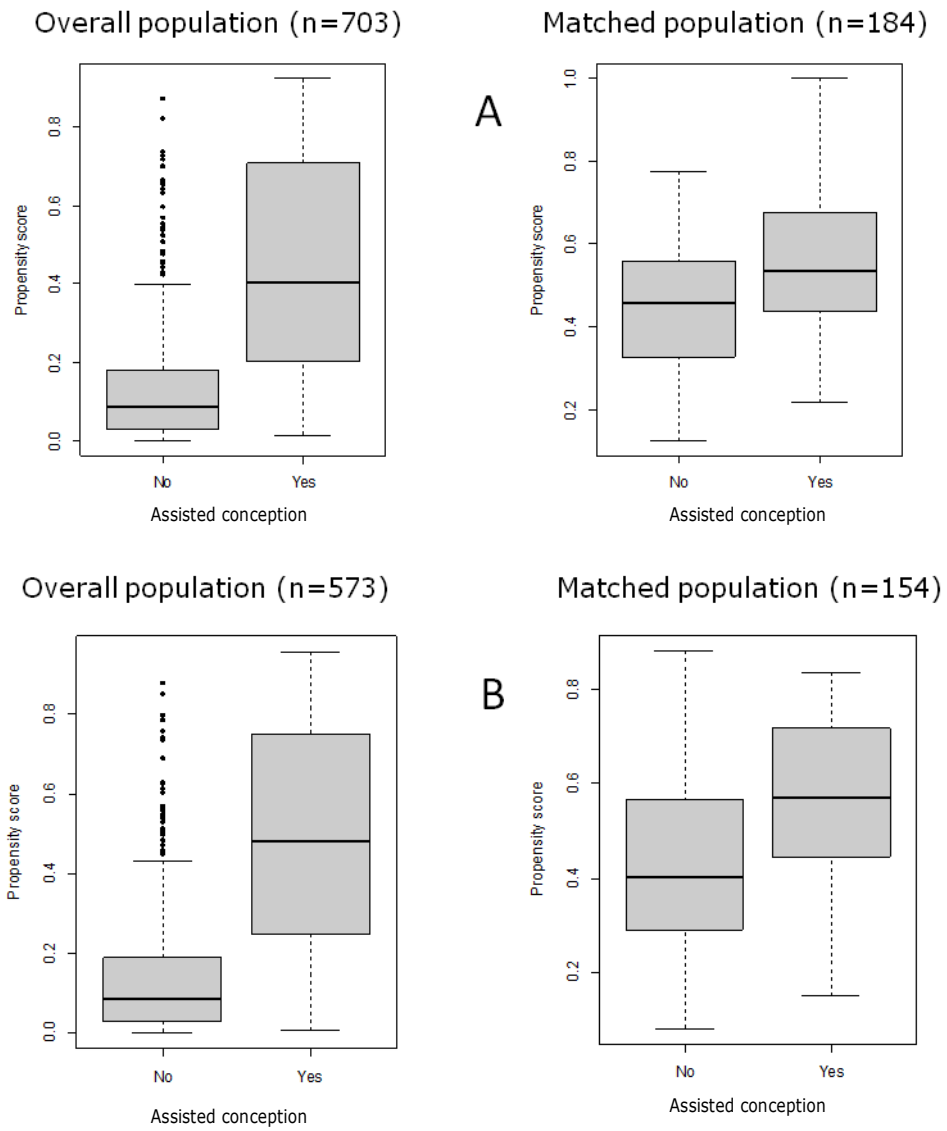

Figure 2. Propensity scores according to the assisted conception status before and after matching for the investigation of (A) the risk of neonatal mortality/morbidity and (B) the risk of non-optimal neurodevelopment at two years of corrected age.

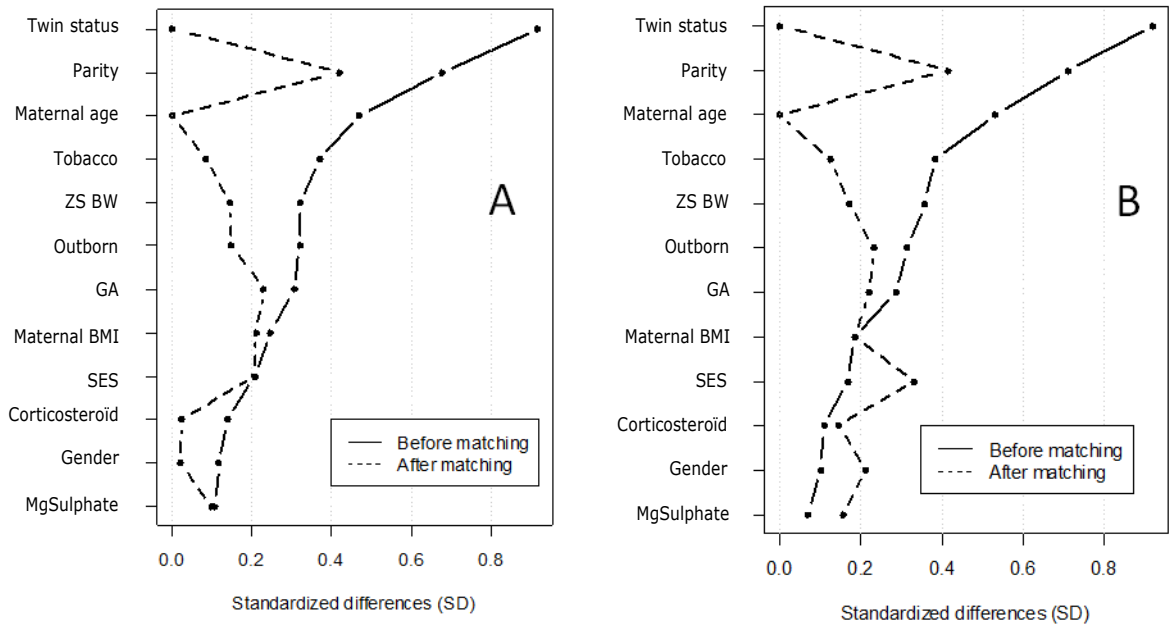

Figure 3. Standardized differences before and after matching for the investigation of (A) the risk of neonatal mortality/morbidity and (B) the risk of non-optimal neurodevelopment at two years of corrected age according to the assisted conception status.

Tobacco: tobacco consumption during pregnancy, ZS BW: z-score of birth weight, Outborn: outborn delivery, GA: gestational age, Maternal BMI: Body Mass Index of the mother, SES: socio-economic status of the mother, Corticosteroïd: antenal corticosteroïd therapy, MgSulphate: antenatal magnesium sulphate therapy

3.2. Neonatal morbidity and mortality

The characteristics of the 703 infants included in the study and of the 184 matched infants for the analysis of morbidity and mortality are presented in Table I. In the overall population, 43.2% of infants were born very preterm (between 28 and 31 weeks GA) and 15.1% were extremely preterm (born before 28 weeks GA). In the overall population, 137 infants (19.5%) were born after AC. Most of them, 76 (55.5%), had been conceived by IVF±ICSI. In the post-matching population, of the 92 infants born after AC, 55 (59.8%) were conceived by IVF±ICSI. Twins were more highly represented in the matched population than in the overall population (54.3% versus 33.0%). Infants with mothers aged between 16 and 24 years were less highly represented in the matched population than in the overall population (6.5% versus 17.4%).

Among the 703 infants included, 37 (5.3%) died before discharge, 32 (4.6%) developed a severe neurological complication (intraventricular haemorrage or periventricular leukomalacia), 114 (16.2%) were treated medically or surgically for patent ductus arteriosus and 8 (1.1%) developed bronchopulmonary dysplasia at 36 weeks corrected GA. Following the matching and adjustment procedure, there was no significant association between neonatal morbidity and mortality and AC: aOR 0.67, 95% CI [0.25, 1.77], p=0.422 (Table II, Figure 4). Extreme prematurity (birth GA less than 28 weeks) was significantly associated with a higher probability of neonatal morbidity and mortality (aOR 128.57, 95% CI [25.31, 653.08], p<0.001) (Table II).

Table I. Characteristics of the overall and matched populations for the analysis of neonatal mortality/morbidity expressed as n (%).

	Overall population N = 703	**Matched population** N = 184
Maternal characteristics		
Maternal age		
16 to 24 years	122 (17.4)	12 (6.5)
25 to 30 years	292 (41.5)	84 (45.7)
31 to 35 years	180 (25.6)	58 (31.5)
36 to 48 years	109 (15.5)	30 (16.3)
Maternal Body Mass Index		
15 to 18.5 kg/m^2	49 (7.0)	17 (9.2)
18.5 to 24.9 kg/m^2	380 (54.1)	87 (47.3)
25 to 57 kg/m^2	224 (31.9)	72 (39.1)
Missing data	50 (7.1)	8 (4.3)
Tobacco consumption during pregnancy	134 (19.1)	22 (12.0)
High socio-economic status of the mother	132 (18.8)	42 (22.8)
Pregnancy characteristics		
Assisted conception	137 (19.5)	92 (50)
IVF ±ICSI	76 (10.8)	55 (29.9)
Ovarian stimulation	28 (4.0)	18 (9.8)
Artificial insemination	16 (2.3)	9 (4.9)
Oocyte donation	17 (2.4)	10 (5.4)
Parity		
1	251 (35.7)	51 (27.7)
2	262 (37.3)	89 (48.4)
3 or more	190 (27.0)	44 (23.9)
Multiple pregnancy	232 (33.0)	100 (54.3)
Antenatal corticosteroïd therapy	466 (66.3)	137 (74.5)
Antenatal magnesium sulphate therapy	178 (25.3)	50 (27.2)
Neonatal characteristics		
Outborn	39 (5.5)	1 (0.5)
Gender of baby: male	382 (54.3)	95 (51.6)
Birth gestational age (GA)		
32 to 34 weeks GA	293 (41.7)	68 (37.0)
28 to 31 weeks GA	304 (43.2)	84 (45.7)
24 to 27 weeks GA	106 (15.1)	32 (17.4)
Z-score of birth weight		
<-1	150 (21.3)	37 (20.1)
[-1, 0]	250 (35.6)	67 (36.4)
[0, 1]	220 (31.3)	64 (34.8)
>1	83 (11.8)	16 (8.7)

IVF: In Vitro Fertilization, ICSI: Intra-Cytoplasmic Sperm Injection

Table II. Risk of neonatal mortality/morbidity according to assisted conception status and the adjustment variables, expressed as odds-ratios with 95% confidence intervals (aOR).

	n (%)	aOR	p value
Assisted conception	92 (50.0)	0.67 [0.25, 1.77]	0,422
Birth gestational age (GA)			
32 to 34 weeks GA	68 (37.0)	1	
28 to 31 weeks GA	84 (45.7)	2.87 [0.65, 12.69]	0,165
24 to 27 weeks GA	32 (17.4)	128.57 [25.31, 653.08]	<0.001
Z-score of birth weight			
< -1	37 (20.1)	0.39 [0.12, 1.26]	0,116
[-1, 0]	67 (36.4)	0.88 [0.30, 2.59]	0,812
[0, 1]	64 (34.8)	1	
> +1	16 (8.7)	0.17 [0.01, 4.04]	0,275
Tobacco consumption during pregnancy	22 (12.0)	0.81 [0.18, 3.61]	0,783
Antenatal magnesium sulphate therapy	50 (27.2)	0.80 [0.31, 2.04]	0,633
Antenatal corticosteroïd therapy	137 (74.5)	0.68 [0.22, 2.11]	0,510
Gender: male	95 (51.6)	0.30 [0.11, 0.82]	0,019
Parity			
1	51 (27.7)	1	
2	89 (48.4)	1.80 [0.55, 5.89]	0,333
3 or more	44 (23.9)	0.35 [0.09, 1.39]	0,137
High socio-economic status of the mother	42 (22.8)	1.09 [0.24, 4.98]	0,915
Maternal Body Mass Index			
15 to 18.4 kg/m^2	17 (9.2)	1	
18.5 to 24.9 kg/m^2	87 (47.3)	5.01 [0.13, 196.14]	0,389
25 to 57 kg/m^2	72 (39.1)	6.90 [0.19, 253.92]	0,294

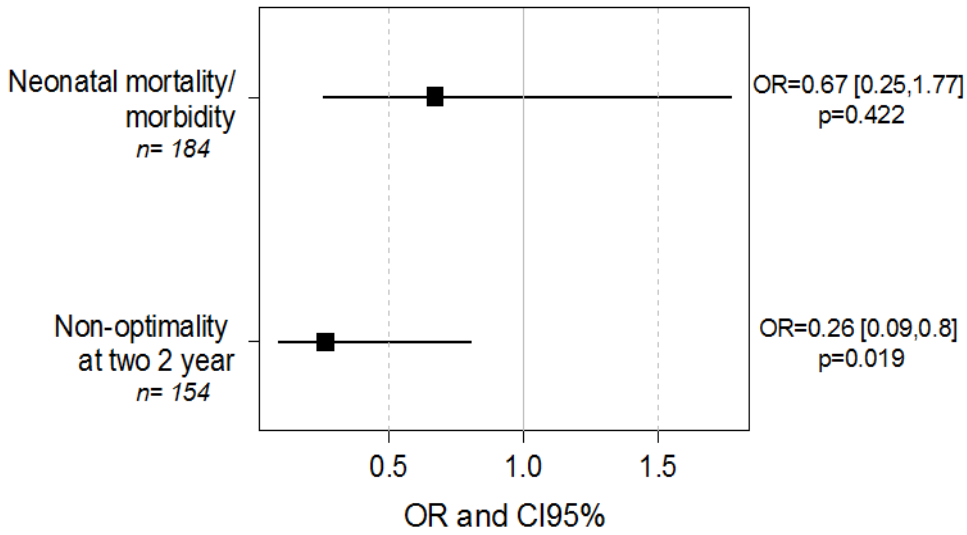

Figure 4. Risk of neonatal mortality/morbidity and non-optimal neurodevelopment at two years of corrected age according to the assisted conception status, expressed as odds-ratios with 95% confidence intervals. Matching on propensity scores with a 0.2 standard deviation caliper and a 1:1 ratio was used. Propensity scores were calculated based on antenatal treatments, gender, gestational age, z-score of birth weight, parity, tobacco consumption during pregnancy, Body Mass Index of the mother and outborn delivery. Finally, exact matching were used for twin status and age of the mother.

3.3. 2-year neurodevelopmental outcome

The characteristics of the 573 infants followed at 2 years and of the 154 infants matched for 2-year neurodevelopment analysis are presented in Table III. Twins were more highly represented in the matched population than in the overall population (50.6% versus 34.0%).

Among the 573 infants followed at 2 years, 85 (14.8%) were regarded as having an overall "non-optimal neurodevelopmental outcome". AC was significantly associated with a reduction in the probability of non-optimal neurological development at 2 years: aOR 0.26, 95% CI [0.09, 0.80], p=0.019 (Table IV, Figure 4). Following the matching procedure, there was no association between neurological development at 2 years and the adjustment variables, in particular birth gestational age, treatments received during pregnancy and the mother's socio-economic status.

93 infants were lost of follow-up before the 2-year neurodevelopmental assessment. The characteristics of these infants and of the 573 infants followed at 2 years are presented in Table V. The proportion of infants born before 28 weeks GA was significantly lower in the lost of follow-up infants (7.5% versus 12.9%, p<0.001). The mothers of the infants lost of follow-up came significantly less frequently from a high socio-economic status (8.6% versus 21.6%, p<0.005).

Table III. Characteristics of the overall and matched populations for the analysis of non-optimal neurodevelopment at two years of corrected age expressed as n (%).

	Overall population N = 573	**Matched population** N = 154
Maternal characteristics		
Maternal age		
16 to 24 years	95 (16.6)	8 (5.2)
25 to 30 years	244 (42.6)	68 (44.2)
31 to 35 years	140 (24.4)	50 (32.5)
36 to 48 years	94 (16.4)	28 (18.2)
Maternal Body Mass Index		
15 to 18.5 kg/m^2	42 (7.3)	14 (9.1)
18.5 to 24.9 kg/m^2	310 (54.1)	83 (53.9)
25 to 57 kg/m^2	183 (31.9)	51 (33.1)
Missing data	38 (6.6)	6 (3.9)
Tobacco consumption during pregnancy	100 (17.5)	20 (13.0)
High socio-economic status of the mother	124 (21.6)	39 (25.3)
Pregnancy characteristics		
Assisted conception	121 (21.1)	77 (50.0)
IVF ±ICSI	69 (12.0)	48 (31.2)
Ovarian stimulation	21 (3.7)	14 (9.1)
Artificial insemination	16 (2.8)	10 (6.5)
Oocyte donation	15 (2.6)	5 (3.2)
Parity		
1	209 (36.5)	39 (25.3)
2	223 (38.9)	81 (52.6)
3 or more	141 (24.6)	34 (22.1)
Multiple pregnancy	195 (34.0)	78 (50.6)
Antenatal corticosteroïd therapy	384 (67.0)	111 (72.1)
Antenatal magnesium sulphate therapy	150 (26.2)	37 (24.0)
Neonatal characteristics		
Outborn	28 (4.9)	5 (3.2)
Gender of baby: male	305 (53.2)	76 (49.4)
Birth gestational age (GA)		
32 to 34 weeks GA	233 (40.7)	51 (33.1)
28 to 31 weeks GA	266 (46.4)	82 (53.2)
24 to 27 weeks GA	74 (12.9)	21 (13.6)
Z-score of birth weight		
<-1	122 (21.3)	28 (18.2)
[-1, 0]	206 (36.0)	63 (40.9)
[0, 1]	179 (31.2)	52 (33.8)
>1	66 (11.5)	11 (7.1)

IVF: In Vitro Fertilization, ICSI: Intra-Cytoplasmic Sperm Injection

Table IV. Risk of non-optimal neurodevelopment at two years of corrected age according to the assisted conception status and the adjustment variables, expressed as odds-ratios with 95% confidence intervals (aOR).

	n (%)	aOR	p value
Assisted conception	77 (50.0)	0.26 [0.09, 0.80]	0.019
Birth gestational age (GA)			
32 to 34 weeks GA	51 (33.1)	1	
28 to 31 weeks GA	82 (53.2)	1.77 [0.39, 8.02]	0.458
24 to 27 weeks GA	21 (13.6)	2.05 [0.25, 17.11]	0.507
Z-score of birth weight			
< -1	28 (18.2)	1.40 [0.37, 5.34]	0.619
[-1, 0]	63 (40.9)	0.45 [0.14, 1.39]	0.164
[0, 1]	52 (33.8)	1	
> +1	11 (7.1)	0.43 [0.02, 8.30]	0.575
Tobacco consumption during pregnancy	20 (13.0)	1.85 [0.43, 8.06]	0.411
Antenatal magnesium sulphate therapy	37 (24.0)	0.53 [0.15, 1.91]	0.335
Antenatal corticosteroïd therapy	111 (72.1)	1.00 [0.30, 3.34]	0.998
Gender: male	76 (49.4)	2.81 [0.86, 9.16]	0.087
Parity			
1	39 (25.3)	1	
2	81 (52.6)	1.04 [0.28, 3.91]	0.950
3 or more	34 (22.1)	0.32 [0.05, 1.99]	0.225
Outborn delivery	5 (3.2)	3.74 [0.25, 56.47]	0.342
High Socio-economic status of the mother	39 (25.3)	0.98 [0.20, 4.76]	0.985
Maternal Body Mass Index			
15 to 18.4 kg/m^2	14 (9.1)	1	
18.5 to 24.9 kg/m^2	83 (53.9)	0.76 [0.14, 4.21]	0.751
25 to 57 kg/m^2	51 (33.1)	0.61 [0.08, 4.38]	0.621

Table V. Comparison of the characteristics of the infants followed at two years of corrected age (n=573) and those lost to follow-up at two years (n=93). Characteristics are expressed as n (%).

	Infants followed at 2-years N = 573	**Infants lost to follow up** N = 93	**p value**
Neonatal morbidity (composite score)	106 (18.5)	15 (16.1)	0,686
Assisted conception	121 (21.1)	12 (12.9)	0,090
Maternel age			0,211
16 to 24 years	95 (16.6)	19 (20.4)	
25 to 30 years	244 (42.6)	32 (34.4)	
31 to 35 years	140 (24.4)	30 (32.3)	
36 to 48 years	94 (16.4)	12 (12.9)	
Maternal Body Mass Index			0,951
15 to 18.5 kg/m^2	42 (7.3)	7 (7.5)	
18.5 to 24.9 kg/m^2	310 (54.1)	53 (57.0)	
25 to 57 kg/m^2	183 (31.9)	27 (29.0)	
Missing data	38 (6.6)	6 (6.5)	
Parity			0,084
1	209 (36.5)	30 (32.3)	
2	223 (38.9)	30 (32.3)	
3 or more	141 (24.6)	33 (35.5)	
Gender : male	305 (53.2)	54 (58.1)	0,450
Multiple pregnancy	195 (34.0)	26 (28.0)	0,301
Birth gestational age (GA)			< 0.001
32 to 34 weeks GA	233 (40.7)	58 (62.4)	
28 to 31 weeks GA	266 (46.4)	28 (30.1)	
24 to 27 weeks GA	74 (12.9)	7 (7.5)	
Z-score of birth weight			0,846
<-1	122 (21.3)	18 (19.4)	
[-1, 0]	206 (36.0)	31 (33.3)	
[0, 1]	179 (31.2)	31 (33.3)	
>1	66 (11.5)	13 (14.0)	
Antenatal magnesium sulphate therapy	150 (26.2)	18 (19.4)	0,202
Antenatal corticosteroïd therapy	384 (67.0)	63 (67.7)	0,985
Outborn delivery	28 (4.9)	9 (9.7)	0,104
Tobacco consumption during pregnancy	100 (17.5)	26 (28.0)	0,053
High socio-economic status of the mother	124 (21.6)	8 (8.6)	0,005

4. Discussion

In our study, we did not find any significant association between AC and neonatal morbidity and mortality in preterm infants born before 34 weeks GA. Moreover, AC was significantly associated with a reduced probability of non-optimal psychomotor development at 2 years of corrected age.

The main difficulty encountered was in ensuring good comparability between infants born after AC or spontaneously conceived. Indeed, many confounders must be taken into consideration. In the study by Xu et al. [27] focussing on factors associated with preterm birth in mothers using AC, mothers who had used AC were significantly older, more socioeconomically fortunate, more frequently primiparae and less frequently smokers. To ensure the best possible comparability between the two groups of infants and to monitor confounders, we opted to match infants conceived or not by AC according to propensity scores, in addition to exact matching according to the mother's age group and twin status (singleton child or twin). We were not able to match monozygotic and dizygotic twins together due to population size. The population size was also insufficient to perform analyses based on the type of fertility treatment used, in particular between those involving gamete or embryo manipulations and the others. The matching process causes a considerable population loss. The lack of significant association between AC and neonatal morbidity and mortality could be related to a lack of power secondary to this population loss. However, even with a small population, we were able to demonstrate a significant effect of AC on neurological outcome at 2 years of corrected age, with an increase in optimality, this over a relatively short period of time (5 years) during which the management of preterm infants changed little. The population loss, following the matching process, changes somewhat the representative character of the population, but the overall and matched populations were compared at each step.

One of the limitations of our study was its monocentric nature. Survival rate at discharge reached 94.7% in our cohort, higher than the EPIPAGE-2 national one [28] reaching 87.6% among infants born alive between 24+0 and 33+6 weeks GA, but also with a fewer proportion of extremely preterm infants. Nevertheless we had the same rate of neurological complications during hospitalisation: 4.6 % in our cohort versus 4.5 % in EPIPAGE 2-study.

Another limitation of this study is the rate of infants lost to follow up (14%) at 2 years of corrected age. Infants lost to follow up were significantly less frequently extremely preterm and their mothers came less frequently from a high socio-economic status.

Concerning neonatal morbidity and mortality, our results are consistent with most previous studies. Five studies have analysed neonatal morbidity and mortality in preterm infants conceived by AC. Among these, the study by Wang et al. [19] had the largest population, with a multicentric retrospective cohort of 21,753 infants born before 32 weeks GA (of which 20,530 infants conceived spontaneously, 953 conceived by IVF±ICSI, 216 born following ovarian stimulation and 54 after intrauterine insemination). This study focused solely on singletons and the analyses were performed separately for each different AC technique used. The rate of birth defect was significantly higher in the "IVF group" (AOR 1.71, 95% CI [1.36, 2.16]) and in the "artificial insemination group" (AOR 3.01, 95% CI [1.47, 6.19]) compared to the "spontaneous conception group". Singletons conceived by IVF±ICSI displayed a higher probability of acute necrotizing enterocolitis (AOR 1.43, 95% CI [1.04, 1.97]) compared to singletons conceived spontaneously, while the other illnesses (hyaline membrane disease, intraventricular haemorrhage, retinopathy), along with mortality, did not differ significantly between groups. There was no significant association between composite death or severe morbidity score and mode of conception in the Canadian study by Chiarelli et al. [20] conducted on preterm singletons ≤32 weeks GA, or in the Canadian study by Shah et al. [23] conducted on multiples ≤32 weeks GA. In the Italian prospective cohort of Corchia et al. [21] with separate analyses of singletons and multiples, survival without major morbidity did not differ significantly between infants born before 32 weeks GA conceived by AC and those conceived spontaneously. Neither Shah et al. nor Corchia et al. were able to take chorionicity into consideration in their analyses of multiples. It should be noted that Picaud et al. [22] were able to demonstrate that AC was significantly associated with an increase in survival without major morbidity (OR 2.256, 95% CI [1.169, 4.356], p=0.0154) compared to spontaneous conception in a population of 602 infants (singletons and multiples). The hypothesis posited for this difference was the probable closer monitoring of pregnancies achieved by AC. One of the strengths of our study was that we were able

to take into account in our analyses the socio-economic status of the mother, tobacco consumption during pregnancy and maternal Body Mass Index.

Few data have been published concerning the 2-year outcome in preterm infants. Only one study has evaluated neurodevelopment at 2-3 years corrected age in infants conceived by AC, though these were more immature than in the population used for our study as they were born at less than 29 weeks GA [24]. In this Australian study by Abdel-Latif et al., the infants underwent a clinical examination, vision and hearing tests, along with GMDS (Griffiths Mental Developmental Scales) and BSID-II (Bayley Scales of Infant Development-II) development evaluations. In the overall population, the proportion of infants born after AC with a functional disability was comparable to that of spontaneously conceived infants (18.9% versus 15.9%, unadjusted OR 1.24, 95% CI [0.85, 1.80], p=0.31). There was a significant association between IVF and the risk of functional disability in infants born between 22 to 26 weeks GA compared to those conceived spontaneously (OR 1.79, 95% CI [1.05, 3.05], p=0.03). Our results are not in agreement with this study as AC was significantly associated with a decrease in non-optimality at 2 years of corrected age, even after having checked for potential confounders, in particular maternal age, the mother's socio-economic status and parity. A possible explanation for this could be the closer follow-up of infants often long-desired and awaited by their parents, along with a more favourable living environment.

5. Conclusion

In our monocentric cohort study, the use of AC was not associated with an increase in neonatal morbidity and mortality and was even significantly associated with a better 2-year neurodevelopmental outcome in preterm infants born before 34 weeks GA. This result is relevant for providing appropriate information to parents considering AC, and more importantly for those with a preterm infant following a pregnancy achieved by AC. Further studies remain necessary to fully confirm these results.

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ANNEXE

Avis du Comité d'Ethique du Centre Hospitalier Universitaire d'Angers

CHU ANGERS
CENTRE HOSPITALIER UNIVERSITAIRE

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COMITE D'ETHIQUE

Pr Christophe Baufreton

Dr Aurore Armand
Département de Médecine d'Urgence
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Angers, le 27 septembre 2017

A Mme Lisa MOLINES

Chère Collègue,

Le Comité d'Ethique du Centre Hospitalier Universitaire d'Angers a examiné dans sa séance du **26 Septembre 2017** votre étude **« Impact des techniques d'assistance médicale à la procréation sur la morbi-mortalité néonatale et le devenir à 2 ans des enfants prématurés nés à moins de 34 semaines d'aménorrhée.»** enregistrée sous le numéro **2017/52**.

Après examen des documents transmis, audition des rapports et discussion, votre projet ne soulève pas d'interrogation éthique.

Cet avis ne dispense toutefois pas le ou les porteurs du projet de s'acquitter des autres obligations réglementaires pouvant être nécessaires.

Je vous prie de croire, Chère Collègue, en l'expression de mes sentiments les meilleurs.

Professeur Christophe Baufreton

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MOLINES Lisa

Impact du mode de conception sur le devenir néonatal et neurodéveloppemental chez les enfants prématurés

RÉSUMÉ

Introduction : L'assistance médicale à la procréation (AMP) augmenterait les naissances prématurées mais peu d'études ont analysé le devenir de ces prématurés. L'objectif de cette étude était d'évaluer l'effet de l'AMP sur la morbi-mortalité néonatale et le devenir neurologique à 2 ans chez des prématurés nés avant 34 semaines d'aménorrhée (SA). **Méthodes :** Tous les enfants nés vivants entre 24^{+0} et 33^{+6} SA et hospitalisés au CHU d'Angers entre janvier 2009 et décembre 2013 étaient éligibles si le caractère spontané ou induit de la grossesse était connu. Les enfants vivants à la sortie d'hospitalisation étaient enrôlés dans la cohorte prospective de suivi LIFT. La morbi-mortalité néonatale était évaluée sur la durée d'hospitalisation selon un score composite incluant décès, hémorragie intra-ventriculaire ≥3, leucomalacie péri-ventriculaire, canal artériel persistant traité et dysplasie broncho-pulmonaire à 36 SA. Le devenir neurologique à 2 ans d'âge corrigé était apprécié par un examen physique, un test neuropsychologique et un questionnaire parental. Pour l'analyse des 2 critères, les enfants étaient appariés 1:1 selon l'âge maternel, la gémellité et le score de propension.

Résultats : 703 enfants ont été inclus pour l'analyse de la morbi-mortalité néonatale, dont 137 nés après AMP. Il n'y avait pas d'association significative entre la morbi-mortalité néonatale et le recours à l'AMP (aOR 0,67 IC 95% [0,25 ; 1,77], p=0,422). 573 enfants ont été suivis à 2 ans dont 121 nés après AMP. Le recours à l'AMP était significativement associé à une diminution de la probabilité de non-optimalité du développement neurologique à 2 ans (aOR 0,26 [0,09 ; 0,80], p=0,019). **Conclusion :** L'AMP n'était pas associée à une augmentation de la morbi-mortalité néonatale et était même significativement associée à un meilleur devenir neurologique à 2 ans chez des enfants prématurés de moins de 34 SA. Des études multicentriques de grande ampleur sont nécessaires pour conforter ces résultats.

Mots-clés : assistance médicale à la procréation, prématurité, morbi-mortalité néonatale, devenir neurologique

Impact of mode of conception on neonatal and neurodevelopmental outcomes in preterm infants

ABSTRACT

Introduction: Assisted conception (AC) appears to increase the rate of premature births, though few studies have analysed outcomes for these preterm infants. The aim of this study was to evaluate the effect of AC on neonatal morbidity and mortality and on neurodevelopmental outcome at 2-years in preterm infants born before 34 weeks of gestational age (GA). **Methods:** All infants born alive between 24^{+0} and 33^{+6} weeks GA and hospitalised at the Angers University Hospital between January 2009 and December 2013 were eligible as long as the mode of conception was known. Live infants at discharge were enrolled in the Loire Infant Follow-up Team (LIFT) prospective longitudinal cohort. Neonatal morbidity and mortality were evaluated during hospitalisation based on a composite score including death, intraventricular haemorrhage grade ≥3, periventricular leukomalacia, treated patent ductus arteriosus and bronchopulmonary dysplasia at 36 weeks GA. The neurodevelopmental outcome at 2-years of corrected age was appreciated by a physical examination, a neuropsychological test and a parental questionnaire. Infants were matched 1:1 according to maternal age, twin status and propensity score. **Results:** 703 preterm infants were included in the analysis of neonatal morbidity and mortality, including 137 born after AC. There was no significant association between AC and neonatal morbidity and mortality (aOR 0.67, 95% CI [0.25, 1.77], p=0.422). 573 infants were assessed at 2 years, including 121 born after AC. AC was significantly associated with a reduction in the probability of non-optimal neurological development at 2 years (aOR 0.26, 95% CI [0.09, 0.80], p=0.019). **Conclusion:** AC was not associated with an increase in neonatal morbidity and mortality and was even significantly associated with a better 2-year neurodevelopmental outcome in preterm infants born before 34 weeks GA. Further studies remain necessary to fully confirm these results.

Keywords : assisted conception, prematurity, neonatal morbidity and mortality, neurodevelopment

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