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Impacto del modo de concepción en los resultados neonatales y del desarrollo neurológico en bebés prematuros

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Resumen e Introducción

Resumen

Pregunta del estudio: ¿Se asocia la concepción asistida con morbilidad y mortalidad neonatal y con deterioro del desarrollo neurológico a los 2 años de la edad corregida en los recién nacidos prematuros nacidos antes de las 34 semanas de edad gestacional?

Respuesta resumida: la concepción asistida no se asocia con un aumento de la morbilidad y la mortalidad neonatales, e incluso se asocia significativamente con un mejor resultado del desarrollo neurológico de 2 años en los recién nacidos prematuros.

Lo que ya se sabe: la concepción asistida parece aumentar la tasa de nacimientos prematuros, aunque pocos estudios han analizado los resultados de estos recién nacidos prematuros.

Diseño del estudio, tamaño, duración: este estudio observacional prospectivo incluyó a 703 bebés prematuros nacidos entre enero de 2009 y diciembre de 2013, y 573 de ellos se evaluaron a los 2 años de la edad corregida.

Participantes / Materiales, Entorno, Métodos: Todos los bebés nacidos vivos entre las 24 + 0 y 33 + 6 semanas de edad gestacional y hospitalizados en el Hospital Universitario de Angers fueron elegibles siempre que se conociera el modo de concepción para la evaluación del resultado neonatal. Se inscribieron en la cohorte longitudinal prospectiva del Equipo de seguimiento de lactantes de Loire (LIFT) y se incluyeron para la evaluación del resultado del desarrollo neurológico. La morbilidad y la mortalidad neonatales se evaluaron durante la hospitalización según un puntaje compuesto que incluyó muerte, hemorragia intraventricular de grado ≥3, leucomalacia periventricular, conducto arterioso persistente tratado y displasia broncopulmonar a las 36 semanas de edad gestacional. El resultado del desarrollo neurológico a los 2 años de la edad corregida se determinó mediante un examen físico, una prueba neuropsicológica y un cuestionario para padres. Con el fin de garantizar la comparabilidad, los bebés fueron emparejados 1:

Principales resultados y el papel del azar: Hubo 703 neonatos prematuros incluidos en el análisis de la morbilidad y mortalidad neonatal, incluidos 137 nacidos después de la concepción asistida. Después de la comparación, se incluyeron 184 neonatos prematuros para el análisis de morbilidad y mortalidad neonatal. No hubo asociación significativa entre la concepción asistida y la morbilidad y la mortalidad neonatales (aOR 0,67; IC del 95% [0,25; 1,77], p = 0,422). Se evaluaron 573 bebés a los 2 años, incluidos 121 nacidos después de la concepción asistida. Después del emparejamiento, se incluyeron 154 neonatos prematuros para el análisis del resultado del desarrollo neurológico. La concepción asistida se asoció significativamente con una reducción en la probabilidad de desarrollo neurológico no óptimo a los 2 años (aOR 0.26, IC 95% [0.09, 0.80], P = 0.019).

Limitación, razones para la precaución: se necesitan más estudios para confirmar completamente estos resultados. Este fue un estudio monocéntrico y el 14% de los bebés inscritos se perdieron durante el seguimiento a los 2 años de la edad corregida.

Implicaciones más amplias de los hallazgos: estos hallazgos son relevantes para proporcionar información adecuada a los padres que consideran la concepción asistida y, lo que es más importante, para aquellos con un bebé prematuro después de un embarazo logrado mediante la concepción asistida.

Fondos de estudio / intereses en competencia: los autores informan sobre fondos externos y no tienen conflictos de intereses para este trabajo.

Número de registro de prueba: N / A.

Introducción

Desde el inicio de la FIV y el nacimiento de Louise Brown en 1978, 6,5 millones de bebés nacieron de la FIV en todo el mundo (Adamson, 2016). En Francia, el INSEE (oficina nacional de estadísticas de Francia) contabilizó 25,208 bebés nacidos después de la concepción asistida en 2014, es decir, el 3,1% de todos los nacimientos en 2014.

Some assisted conception-related effects are now known and supported by extensive publications, including several meta-analyses. Independently of the increase in twin status, assisted conception appears to increase the risk of preterm and very preterm birth, low birth weight (LBW) and infants being born small for gestational age (SGA) (Helmerhorst *et al.*, 2004; Jackson *et al.*, 2004; McDonald *et al.*, 2009; Hayashi *et al.*, 2012; Pandey *et al.*, 2012; Pinborg *et al.*, 2013; Ombelet *et al.*, 2016). According to a large cohort study, births of preterm singletons increase significantly in cases of IVF conception, with or without ICSI and after conception following ovarian stimulation alone, in comparison to naturally conceived singletons (Ombelet *et al.*, 2016). Moreover, several studies have reported an increase in the risk of birth defects following IVF conception (Kallen *et al.*, 2010; Davies *et al.*, 2012; Wen *et al.*, 2012; Hansen *et al.*, 2013; Boulet *et al.*, 2016).

The neurodevelopmental outcome in infants born after assisted conception has also been studied (Strömberg *et al.*, 2002; Ponjaert-Kristoffersen *et al.*, 2005; Hashimoto *et al.*, 2016). A study by Ponjaert-Kristoffersen *et al.* failed to show any differences in cognitive or motor development at 5 years (Ponjaert-Kristoffersen *et al.*, 2005). 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 (Strömberg *et al.*, 2002).

Only five studies (of which three were retrospective) have analysed neonatal morbidity and mortality in preterm infants born after assisted conception, although they failed to show any differences in survival without major morbidity (Shah *et al.*, 2011; Picaud *et al.*, 2012; Corchia *et al.*, 2014; Chiarelli *et al.*, 2015; Wang *et al.*, 2017). Only one study analysed the neurodevelopmental outcome in preterm infants born after assisted conception, but this study focused on extremely premature infants (born before 29 weeks of gestational age (GA)) (Abdel-Latif *et al.*, 2013).

The aim of this study was to assess 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 of gestational age (GA).

Materials and Methods

Study Setting and Population

This was 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 were enroled in the Loire Infant Follow-up Team (LIFT) follow-up programme. Infants with malformative pathologies including congenital heart disease, abdominal wall defects, gastric atresia, antenatal brain malformations and genetic syndrome were excluded. Infants whose parents 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 enroled in the LIFT network. The clinical data for infants who died 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 (Olsen *et al.*, 2010). The following pregnancy-related maternal data were collected retrospectively from the medical records for all infants: mode of conception and technique used if assisted conception (ovarian stimulation, intrauterine insemination, IVF with or without ICSI), maternal body mass index (BMI) at onset of pregnancy, socio-economic status (INSEE classification), universal health coverage (CMU: Couverture Médicale Universelle) and smoking before and during pregnancy.

Ethical Approval

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.

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).

Secondary Outcome

The secondary outcome was non-optimal neurodevelopment at 2 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 (Flamant *et al.*, 2011). Infants with non-optimal neuromotor and/or psychomotor assessments were regarded as having an overall 'non-optimal neurodevelopmental outcome'.

Statistical Analysis

To ensure comparability between infants who were conceived by assisted conception and those who were naturally conceived, these two populations were matched. Indeed, these differences could lead to major bias because of the known characteristics of mothers who need fertility treatment. For both analyses, risk of neonatal mortality/morbidity and risk of non-optimal neurodevelopment at 2 years of age, infants were matched on propensity scores with a 0.2 SD 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 were calculated with variables usually associated (positively or negatively) with assisted conception: GA (32–34, 28–31 and 24–27 weeks GA), z-score of birth weight (<−1, −1 to 0, 0 to 1 and >+1 SD SD), antenatal treatments (corticosteroids and magnesium sulphate), gender, parity (1, 2 and 3 or more), BMI of the mother (15–18.4, 18.5–24.9 and 25–57 kg/m^2), tobacco consumption of the mother during pregnancy

(yes versus no), outborn delivery (i.e. not at a tertiary-care medical centre) (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 standardised differences.

The possible effects of assisted conception on the risk of neonatal mortality/morbidity and on the risk of non-optimal neurodevelopment at 2 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.

Results

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 were not 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. After this, 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 assisted conception and those conceived naturally, the infants were matched: Figs 2 and 3 show population comparability before and after matching according to propensity score (Figure 2) and standardised differences (Figure 3).

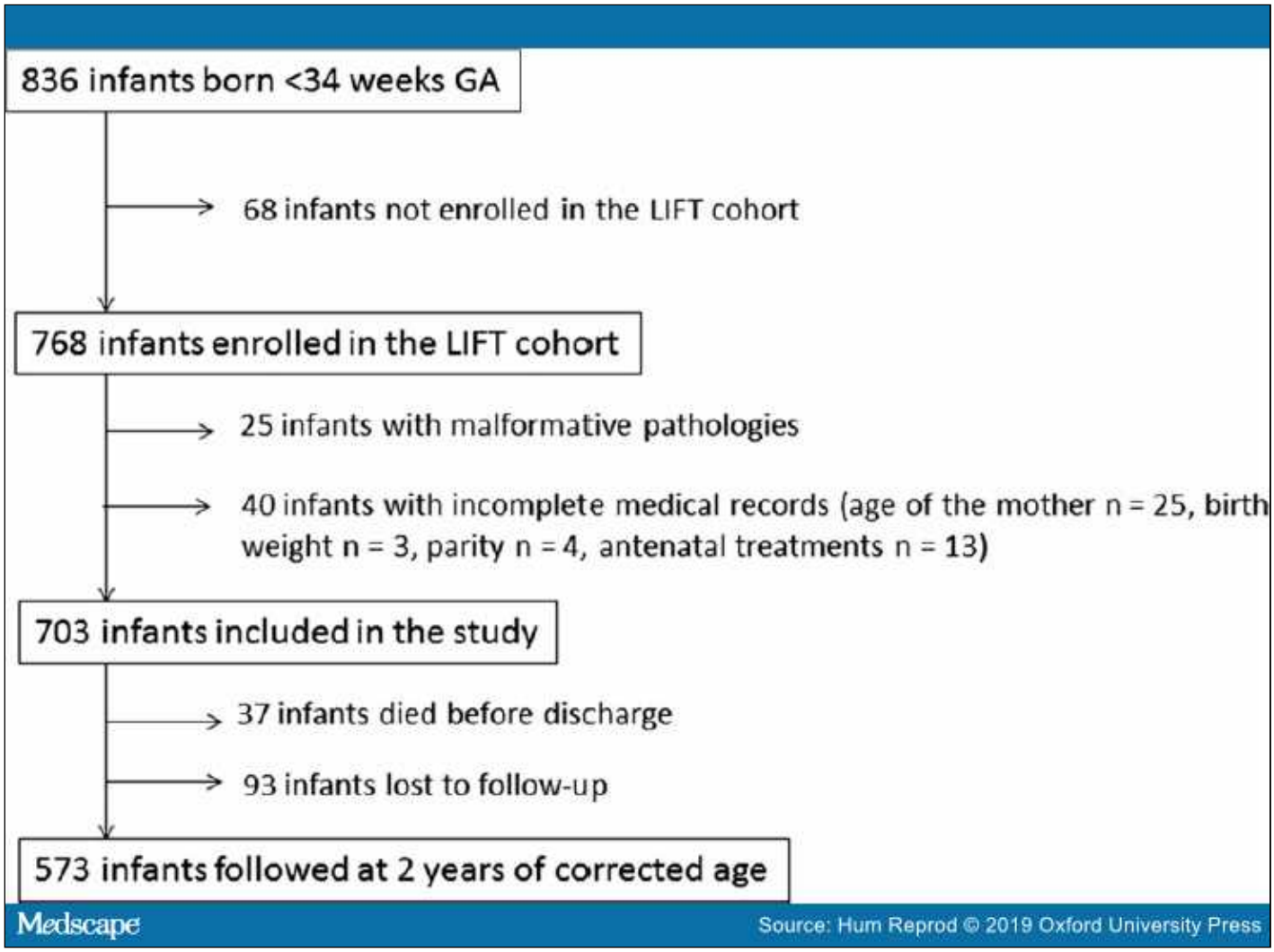

Figure 1.

Flowchart of study participants.

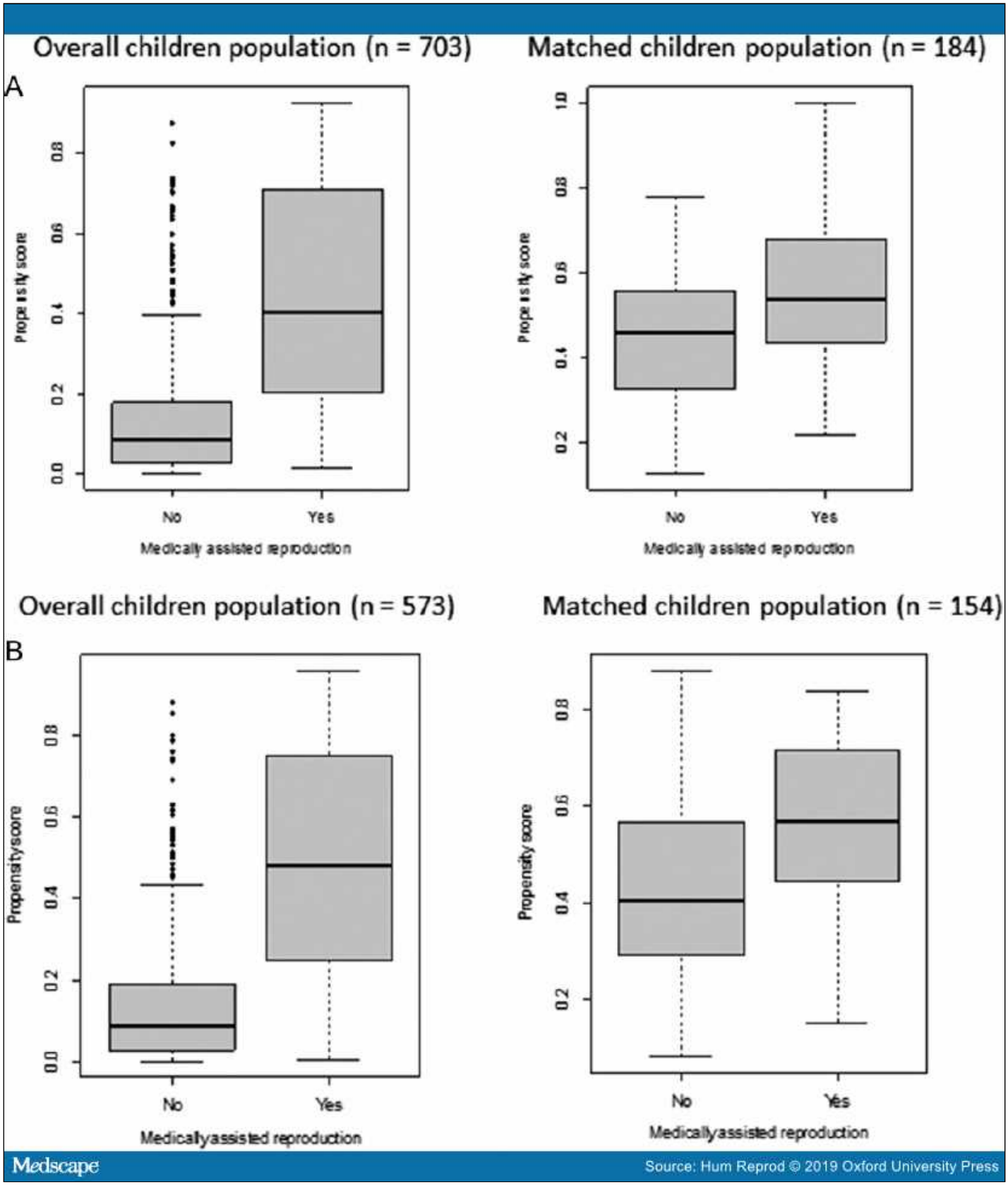

Figure 2.

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

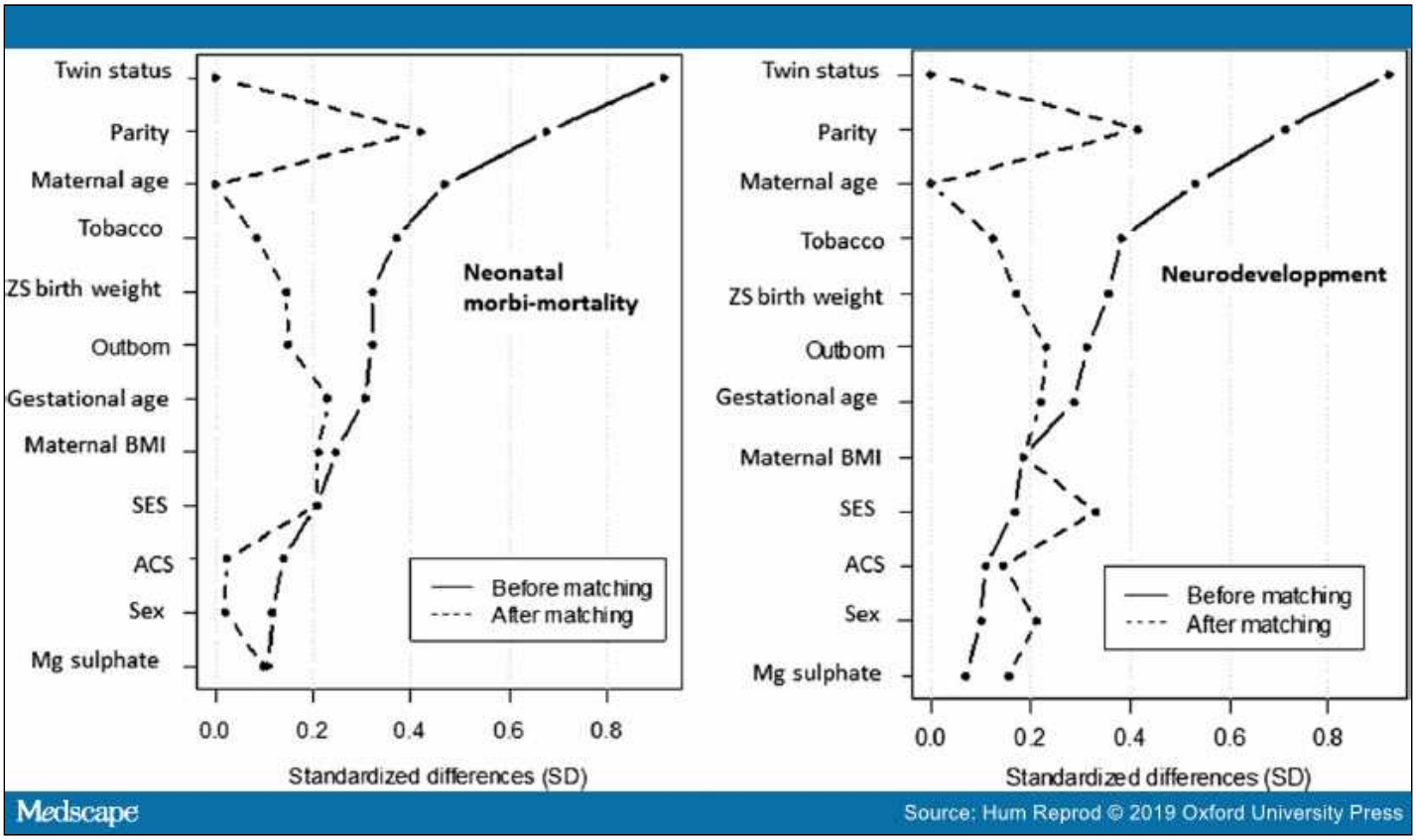

Figure 3.

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

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 . 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 assisted conception. Most of them, 76 (55.5%), had been conceived by IVF±ICSI. In the post-matching population, of the 92 infants born after assisted conception, 55 (59.8%) were conceived by IVF±ICSI. Multiple pregnancies 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 assisted conception: aOR 0.67, 95% CI [0.25, 1.77], $P = 0.422$ (, 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 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)
Spontaneous preterm delivery**	377 (53.6)	101 (54.9)
Neonatal characteristics		
Outborn delivery	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)

*Complete course of betamethasone.
**Preterm labour and/or premature rupture of membranes.

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

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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
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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	
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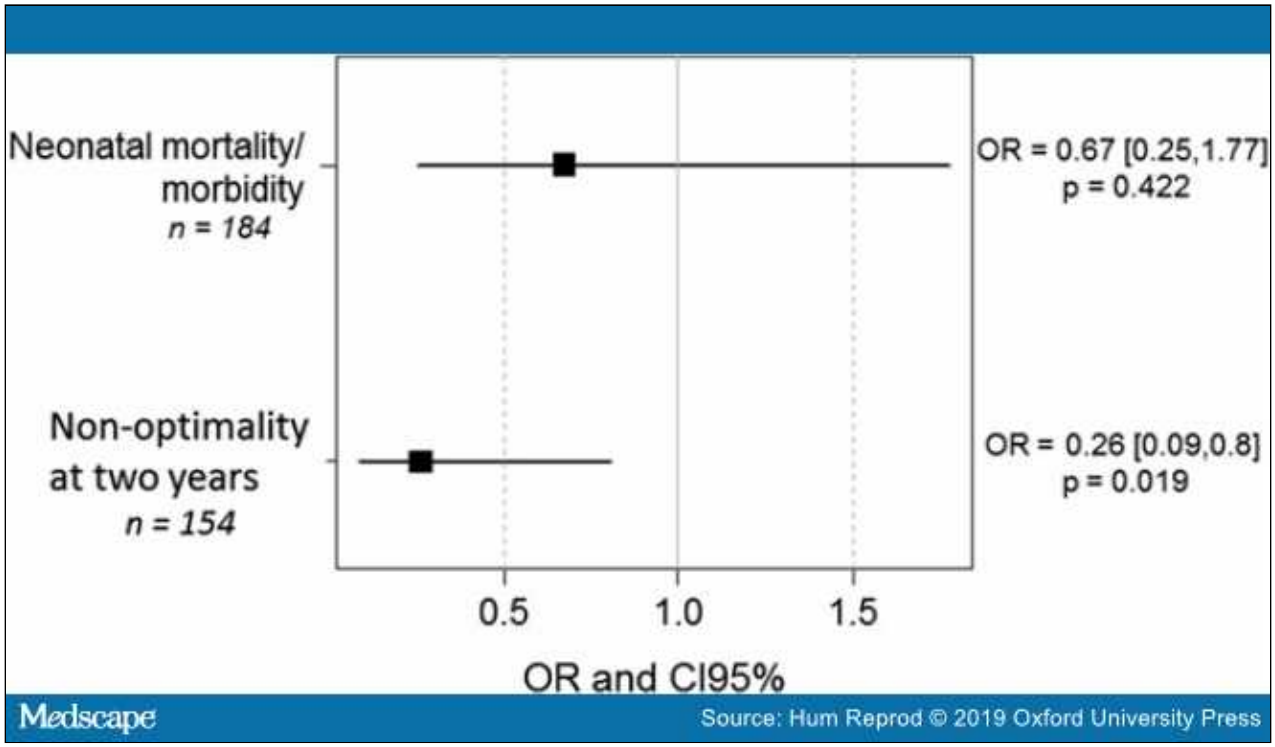

Figure 4.

Risk of neonatal mortality/morbidity and nonoptimal neurodevelopment at 2 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 SD 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 delivery outside a tertiary care centre. Finally, exact matching were used for twin status and age of the mother.

Two-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 . Multiple pregnancies 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'. Assisted conception was significantly associated with a reduced probability of non-optimal neurological development at 2 years: aOR 0.26, 95% CI [0.09, 0.80], $P = 0.019$ (, 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. There were 93 infants 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 . 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 to 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 2 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)
Spontaneous preterm delivery**	303 (52.9)	81 (52.6)
Neonatal characteristics		
Outborn delivery	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)

*Complete course of betamethasone.
**Preterm labour and/or premature rupture of membranes.

Table IV. Risk of non-optimal neurodevelopment at 2 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 2 years of corrected age (*n* = 573) and those lost to follow-up at 2 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

Discussion

In our study, we did not find any significant association between assisted conception and neonatal morbidity and mortality in preterm infants born before 34 weeks GA. Moreover, assisted conception 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 assisted conception or naturally conceived infants. Indeed, many confounders must be taken into consideration. In a recent study focussing on factors associated with preterm birth in mothers using assisted conception, mothers who had used assisted conception were significantly older, more socioeconomically fortunate, more frequently primiparae and less frequently smokers (Xu *et al.*, 2014). 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 assisted conception 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 assisted conception 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 assisted conception on neurological outcome at 2 years of corrected age, with an increase in optimality, and 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 rate of 87.6% among infants born alive between 24 + 0 and 33 + 6 weeks GA, but also with a lower proportion of extremely preterm infants (Ancel *et al.*, 2015). 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.

Regarding the possible effect between assisted conception and neonatal morbidity, our study did not allow us to conclude whether there is no effect of assisted conception or if the sample size is too low; therefore, further research with larger sample size is needed. Nevertheless our results are consistent with most previous studies. Five studies have analysed neonatal morbidity and mortality in preterm infants conceived by assisted conception. Among these, the study by Wang and al. had the largest population, with a multicentric retrospective cohort of 21,753 infants born before 32 weeks GA (of which 20,530 infants were conceived naturally, 953 were conceived by IVF±ICSI, 216 were born following ovarian stimulation and 54 were born after intrauterine insemination) (Wang *et al.*, 2017). This study focused solely on singletons and the analyses were performed separately for each different assisted conception technique used. The rate of birth defects 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 necrotising enterocolitis (AOR 1.43, 95% CI [1.04, 1.97]) compared to singletons conceived naturally, 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 a Canadian study conducted on preterm singletons ≤32 weeks GA, or in a Canadian study conducted on multiple births ≤32 weeks GA (Shah *et al.*, 2011; Chiarelli *et al.*, 2015). In an Italian prospective cohort with separate analyses of singletons and multiples, survival without major morbidity did not differ significantly between infants born before 32 weeks GA conceived by assisted conception and those conceived naturally (Corchia *et al.*, 2014). Neither the Canadian nor the Italian study were able to take chorionicity into consideration in their analyses of multiples. It should be noted that another French Cohort study was able to demonstrate that assisted conception 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 naturally conception in a population of 602 infants (singletons and multiples) (Picaud *et al.*, 2012). The hypothesis posited for this difference was the probable closer monitoring of pregnancies achieved by assisted conception. 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 BMI.

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 assisted conception, although these were more immature than in the population used for our study as they were born at less than 29 weeks GA (Abdel-Latif *et al.*, 2013). In this Australian study, 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 assisted conception with a functional disability was comparable to that of naturally conceived infants (18.9% versus 15.9%, unadjusted OR 1.24, 95% CI [0.85, 1.80], $P = 0.31$), but there was a significant association between IVF and the risk of functional disability in infants born between 22 and 26 weeks GA compared to those conceived naturally (OR 1.79, 95% CI [1.05, 3.05], $P = 0.03$). Our results are not in agreement with this study as assisted conception 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.

Conclusion

In our monocentric cohort study, the use of assisted conception 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 assisted conception, and more

importantly for those with a preterm infant following a pregnancy achieved by assisted conception. Further studies remain necessary to fully confirm these results.

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