Neurodevelopment at 5 years of age for preterm-born children according to mode of conception: a cohort study

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GYNECOLOGY

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BACKGROUND: Preterm delivery is a risk factor for suboptimal neurodevelopment. Pregnancies conceived after medically assisted reproduction—which includes in vitro fertilization, with or without intracytoplasmic insemination, and induction of ovulation followed by intrauterine insemination or timed intercourse—have a higher risk of preterm delivery. Few studies have evaluated the outcome at >2 years of age of such preterm-born children.

OBJECTIVE: To evaluate neurodevelopmental outcome at $5^1/_2$ years of age of children born preterm according to the mode of conception (spontaneous vs medically assisted reproduction).

STUDY DESIGN: A total of 4349 children born between 24 and 34 weeks of gestation who survived to $5^1/_2$ years of age in the 2011 French prospective national cohort study "EPIPAGE-2" were included: 814 in the medically assisted reproduction group (433 by in vitro fertilization, with or without intracytoplasmic insemination, and 381 by induction of ovulation) and 3535 in the spontaneously conceived group. The studied neurodevelopmental outcomes were sensory (hearing and vision) impairments, cerebral palsy, cognition, and developmental coordination disorders. Multivariate analyses were performed with generalized estimating equation models adjusted for gestational age, antenatal steroids, and social characteristics. All analyses were performed following multiple imputation. Sensitivity analyses were performed with the populations of singletons and cases with complete data.

RESULTS: No differences in cerebral palsy (adjusted odds ratio, 1.00; 95% confidence interval, 0.67—1.49), neurodevelopmental impairment (adjusted odds ratio, 1.09; 95% confidence interval, 0.82—1.45), or developmental coordination disorders (adjusted odds ratio, 0.75; 95% confidence interval, 0.50—1.12) were found between children born following medically assisted reproduction and children born following spontaneous conception after adjustment for sociodemographic factors. For proportions of children with an intelligence quotient below 1 and 2 standard deviations, there were no differences between those born after medically assisted reproduction and those born after spontaneous pregnancy (respectively, adjusted odds ratio, 0.99; 95% confidence interval, 0.80—1.23 and adjusted odds ratio, 1.14; 95% confidence interval, 0.83—1.56). In subgroup analyses, no differences were observed between children born following induction of ovulation or in vitro fertilization and those conceived spontaneously. Sensitivity analyses were consistent with the main results.

CONCLUSION: In this cohort of preterm-born children, there was no evidence of an impact of the mode of conception on neurodevelopmental outcomes at $5^1/_2$ years of age.

Key words: medically assisted reproduction, neurodevelopment, preterm birth

Introduction

Infertility, defined as inability to conceive after 1 year of regular, unprotected sexual intercourse,[1] affects approximately 15% of couples.[2] This has many consequences, including sexual dysfunction, social stigmatization, and relationship breakdown.[3–8] Since the birth of the first child conceived through in vitro fertilization (IVF) in 1978, the use of assisted reproductive technologies (ARTs) has increased substantially, such that 3% to 4% of births are now from pregnancies conceived through ART.[9,10] However, ART includes only the in vitro handling of oocytes and sperm, or of embryos, thus including IVF and IVF with intracytoplasmic sperm injection (ICSI) but not intrauterine insemination (IUI) following induction of ovulation (IO) or timed intercourse (TIC) following IO.[1] These techniques, which fall under the broader term of "medically-assisted reproduction" (MAR),[1] also expose women and fetuses to exogenous hormones.

A major concern for women undergoing MAR and their partners is long-term neurodevelopmental outcome of the offspring. Problems potentially arise because genes subject to parental imprinting may be affected by epigenetic modifications relating to MAR (hormonal IO, manipulation of male gametes, IVF, or embryo transfer), thus negatively affecting the offspring.[11] MAR is also associated with both an increased risk of preterm birth (at <37 weeks of gestational age [GA]), including very preterm birth (at <32 weeks' GA),[12] and with multiple pregnancy (particularly following multifollicular stimulation or multiple embryo transfers), which is itself associated with preterm birth.[10] Preterm birth is in turn associated with a risk of poorer neurodevelopmental outcomes.[13–15] To date, however, data concerning the neurodevelopment of children born following MAR have been inconsistent, with studies finding

Cite this article as: Verhaeghe C, Marchand-Martin L, Kaminski M, et al. Neurodevelopment at 5 years of age for preterm-born children according to mode of conception: a cohort study. Am J Obstet Gynecol 2022;XX:x.ex—x.ex.

0002-9378

https://doi.org/10.1016/j.ajog.2022.05.062

AJOG at a Glance

Why was this study conducted?

Some studies have suggested that children born preterm following medically assisted reproduction (MAR) are at additional risk for neurodevelopmental impairments. These have mostly focused on outcomes at up to 2 years of age, but evidence at older ages is lacking.

Key findings

In this prospective cohort, there were no differences in neurodevelopmental outcomes—including cognition, cerebral palsy, combined neurosensory impairment, and developmental coordination disorders—at $5^1/_2$ years of age between children born preterm after MAR and those conceived naturally when results were fully adjusted for sociodemographic factors.

What does this add to what is known?

MAR is not associated with additional long-term neurodevelopmental impairments at up to $5^1/_2$ years of age for children born preterm.

outcomes in children conceived following MAR compared with children conceived naturally to be poorer,[16] better,[17,18] or the same.[12,19] Such discrepancies arise because of differences in neurodevelopmental domains studied and age at follow-up, and methodological differences between the studies[20]; the true impact of MAR therefore remains unclear.[12]

When looking more specifically at neurodevelopment in children born preterm following MAR, few data are available. Two retrospective population-based studies of births before 29 weeks' GA assessed at 18 to 24 months found conflicting results,[18,21] whereas a single-center study of births before 34 weeks found a reduced probability of poor neurodevelopment at 2 years of age.[22] Only 1 study has examined outcomes after at least 5 years of age—and only in relation to cerebral palsy—and found no differences by mode of conception.[23] However, neurodevelopment is dynamic and evolves over time: motor deficits become apparent first, with cognitive deficits appearing later. By age 5, more subtle defects are detectable, thus multiple dimensions of development should be studied. We sought to evaluate the impact of mode of conception on neurodevelopment at $5^1/_2$ years of age in children born at <35 weeks' GA. Our primary objective was to assess whether any effect on neurodevelopment was evident using all MAR techniques combined. Different techniques may also have different effects: IVF or IVF-ICSI techniques, such as multifollicular stimulation, gamete manipulation, embryo culture, and embryo transfer, might cause epigenetic disturbances; these might also be observed following hormonal stimulation (IO with TIC, or IUI).[11] We therefore studied subgroups of children born following the use of these techniques in comparison with those born after spontaneous conception. We hypothesized that there would be no differences once social factors were accounted for.

Materials and Methods

Setting and data collection

The French prospective, national cohort study "EPIPAGE-2" collected information about all births at <35 weeks' GA in 546 maternity hospitals in France in 2011.[24,25] Children born at <27 weeks' GA were recruited over 8 months (equivalent to 35 weeks), those born between 27 and 31 completed weeks of GA over 6 months (equivalent to 26 weeks), and those between 32- and 34-weeks' GA over 5 weeks. At birth, maternal, obstetrical, and neonatal data were obtained from medical records, and during the child's hospital stay, mothers were interviewed to obtain information on their social characteristics and pregnancy. Surviving children were seen by trained investigators at $5^1/_2$ years of age: this included a medical examination and neuropsychological assessment, and parents completed a questionnaire.

Population

Only children born between 24- and 34-weeks' GA were included because the 1 child born at <24 weeks who survived was lost to follow-up at $5^1/_2$ years. We excluded children for whom mode of conception or, if born following MAR, type of infertility treatment were unknown.

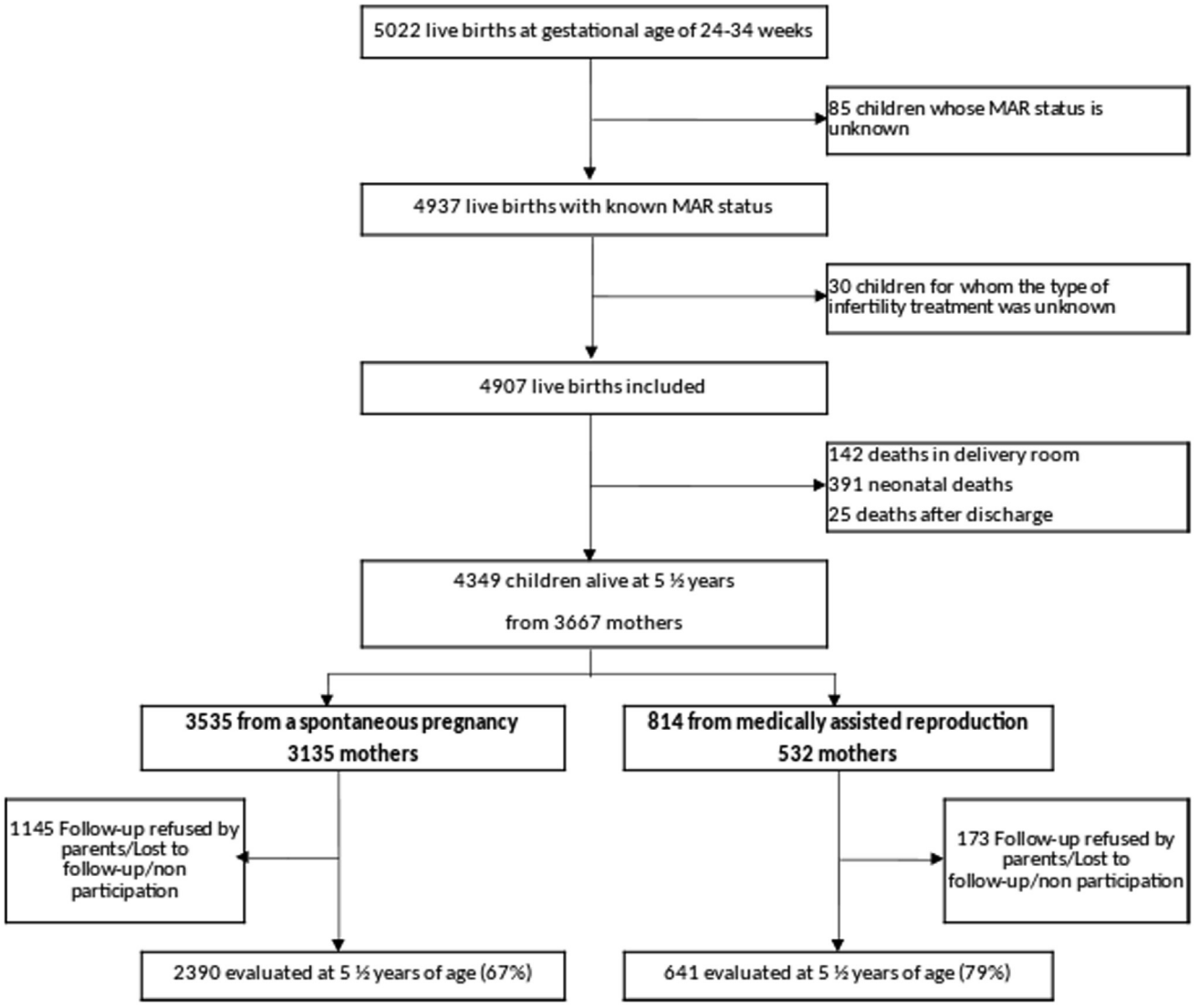
Exposure

Birth following MAR was compared with that following spontaneous conception. Information about MAR was collected at birth from medical notes and postnatal interview; the use of hormonal stimulation (IO with TIC, or IUI) or IVF (alone or with ICSI) were accepted as evidence of an MAR-conceived pregnancy. The subgroups of IO with TIC or IUI, and IVF or IVF-ICSI were also examined separately.

Main outcomes

We studied cerebral palsy, sensory (hearing and vision) and cognitive impairments, and developmental coordination disorders. Cerebral palsy was diagnosed clinically using the Surveillance of Cerebral Palsy in Europe network criteria and classified according to the Gross Motor Function Classification System (GMFCS). Visual impairment was defined as binocular visual acuity <3.2/10, and hearing impairment was defined as uni- or bilateral hearing loss >40 dB not corrected or only partially corrected with hearing aids. Cognitive ability was measured using the full-scale intelligence quotient (FSIQ) from the Wechsler Preschool and Primary Scale of Intelligence—Fourth Edition (WPPSI-IV, French version)[26]; this composite score is obtained from 5 domains: verbal comprehension, visuospatial indices, fluid reasoning, working memory, and processing speed. We studied mean intelligence quotient (IQ) and proportions of children with scores both 1 and 2 standard deviations (SDs) below the mean of a reference group of

FIGURE
Flowchart



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children born at term (37–41 weeks' GA). The reference group, weighted to be representative of the French population, was selected from a contemporaneous birth cohort, with children undergoing the same follow-up as those in EPIPAGE-2.[27] Moderate to severe impairment was defined as having at least 1 sensory impairment, cerebral palsy GMFCS level 2 or higher, or FSIQ >2 SDs below the mean of the reference group. Finally, developmental coordination disorders were assessed in children without moderate or severe impairment using the Movement Assessment Battery for Children, Second Edition. We studied both total scores and using a cutoff score below the fifth percentile (relative to the reference group).

Other studied factors

Maternal characteristics available from delivery were: maternal age (years), level of education (less than high school, high school, 1–2 years or >2 years of graduate study), currently employed (yes/no), birth country (France or elsewhere), cohabitation status, smoking during pregnancy (yes/no), and household socioeconomic status defined according to the highest status of the mother and partner, or mother only if she lived alone (executive, intermediate, administration, service and trade, manual worker, and unemployed). Obstetrical variables were: parity (nulliparous or not), singleton or multiple pregnancy, induced or spontaneous labor, delivery mode (vaginal or cesarean), receipt of antenatal steroids and tocolysis, and neonatal unit level at delivery hospital. Neonatal characteristics were: GA at delivery (completed weeks), sex, small for GA (using French reference

curves[28]), and severe malformations (yes/no).

Statistical analysis

Population characteristics were described using means and SDs for continuous variables, with groups compared using Student or Wilcoxon tests. For categorical variables, we described proportions and used chi square or Fisher exact tests. Mortality rates between birth and follow-up were assessed to determine whether there were differences in survival between children conceived following MAR and those conceived spontaneously. Regression analyses were performed among survivors aged $5^1/_2$ years. For binary outcomes, odds ratios were estimated with logistic regression, and for continuous outcomes, linear regression was used; both used generalized estimating equations (GEE) to account for nonindependence of multiple children born to the same mother. We first estimated crude associations, then added GA at birth and antenatal steroids to explore any potential mediating impact from these factors, and finally, in the fully adjusted model, included sociodemographic variables that were considered a priori to be potential confounders. These were: maternal age, parity, birth country, level of education, employment, smoking during pregnancy, cohabitation, and socioeconomic status. A P value $<.05$ was considered statistically significant; results are presented with 95% confidence intervals (CIs).

Data were weighted according to GA group by a factor of 1.34 (35/26) for children born at 27 to 31 weeks and by a factor of 7 (35/5) for those born at 32 to 34 weeks to account for the differing recruitment periods, and multiple imputation was performed using chained equations to account for missing outcome data; imputation models included variables potentially predicting nonresponse or the outcome (Supplemental Table 1). Estimates were combined using Rubin's rules.[29] All investigations were conducted using R, version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria).[30] GEE models were performed using the R package "geepack"[31] and multiple imputation with the package "mice."[32]

Sensitivity analyses

We did not adjust for multiple pregnancy status because this potentially lies on the causal pathway between MAR and later outcome. Instead, we repeated analyses using singleton births only. We also performed sensitivity analyses of all models on the population of children with complete data.

Ethical approvals

Data were collected with permission from the Commission Nationale de l'Informatique et des Libertés (National Data Protection Authority—reference: 911009) and from the relevant ethics committees (Consultative Committee on the Treatment of Data on Personal Health for Research Purposes—reference: 10.626; Committee for the Protection of People Participating in Biomedical Research—reference: CPP SC-2873). Mothers gave verbal consent to provide data following delivery, and written consent was obtained for follow-up.

Results

Study population

At 24 to 34 completed weeks' GA, 5022 children were born alive; mode of conception, including type of infertility treatment, was known for 4907. Of these, 558 children died before reaching $5^1/_2$ years of age (4.6% in the MAR and 6.0% in the non-MAR group, P=.025). Among the 4349 survivors, complete information was available for 641 of 814 children born following MAR and 2390 of 3535 children born following spontaneous pregnancy. More children were lost to follow-up from spontaneous and singleton pregnancies and from families of lower socioeconomic status, and their mothers were more often younger, multiparous, single, smokers, and born outside of France (Figure; Supplemental Tables 2 and 3).

Baseline characteristics

MAR was used by 532 mothers; at delivery, these mothers were older, more highly educated, more often employed, of higher socioprofessional category, and less frequently smokers than women with spontaneous pregnancies (Table 1). Their children were more often from multiple pregnancies, small for GA, exposed to antenatal steroids, and born following spontaneous labor, with noncephalic presentation, and in hospitals with level 3 neonatal intensive care units. There were no differences in terms of GA, sex, presence of severe malformations, or mode of delivery (Table 2).

Outcomes at $5^1/_2$ years of age

At $5^1/_2$ years of age, before adjustment, there were better outcomes for cognition among children born following MAR than among those from spontaneous pregnancies (Table 3). These differences disappeared following adjustment with sociodemographic variables (Table 4). Similar results were observed for the composite measure of moderate to severe neurodevelopmental impairment. There were no differences in unadjusted or adjusted analyses for cerebral palsy, nor in proportions of sensory deficiencies, between children born following MAR and children from spontaneous pregnancy (Table 3), nor were any differences identified for developmental coordination disorders (Tables 3 and 4).

Subgroup analyses

For both the children born following IO or IUI and those born following IVF or IVF-ICSI, similar patterns to those observed in the main analysis were noted. In both groups, the mean IQ before adjustment was higher than that of children born from spontaneous pregnancies, and fewer children had an IQ <1 SD (Table 3); the proportion of children with an IQ <2 SDs was also lower in the IVF/IVF-ICSI group but not in the IO/IUI group. Again, after adjustment for sociodemographic factors, no differences persisted (Table 4).

Sensitivity analyses

Results for singleton analyses were consistent for all outcomes among the entire population (Supplemental Table 4). In subgroup analyses, the odds ratio for having an FSIQ <1 SD

TABLE 1
Characteristics of the 3667 mothers with children in the EPIPAGE-2 cohort surviving to 5½ years of age according to mode of conception, after multiple imputation

Characteristic	Spontaneous N mothers=3135	MAR[a] N mothers=532	IO or IUI N mothers=254	IVF or IVF-ICSI N mothers=278
Age, mean (95% confidence interval)	29.4 (29.2–29.7)	32.0 (31.5–32.6)	31.4 (30.4–32.3)	32.6 (32.0–33.2)
Primiparous	49.9 (47.5–52.3)	77.0 (72.3–81.8)	74.8 (67.8–81.7)	79.0 (72.4–85.6)
Born in France	78.8 (76.9–80.7)	84.8 (81.0–88.6)	85.5 (80.3–90.8)	84.1 (78.6–89.6)
Smoked during pregnancy	23.5 (21.5–25.5)	8.8 (5.5–12.1)	9.2 (4.5–14.0)	8.4 (3.8–13.0)
Level of education				
Less than high school	36.7 (34.4–39.0)	22.1 (17.3–27.0)	25.7 (18.1–33.3)	19.0 (12.8–25.2)
High school	23.3 (21.3–25.4)	15.9 (11.7–20.1)	15.4 (9.7–21.1)	16.3 (10.3–22.3)
1–2 y of graduate studies	17.9 (16.0–19.8)	21.0 (16.3–25.6)	23.7 (16.4–31.0)	18.6 (12.8–24.4)
≥3 y of graduate studies	22.0 (20.0–24.1)	41.0 (35.3–46.8)	35.2 (27.0–43.4)	46.1 (38.1–54.0)
Occupational activity during pregnancy	61.7 (59.4–64.0)	80.1 (75.5–84.6)	74.7 (67.3–82.0)	84.8 (79.2–90.3)
Cohabiting with partner at delivery	88.9 (87.4–90.4)	97.3 (95.4–99.2)	96.5 (93.4–99.5)	98.1 (95.8–100)
Parents' socioeconomic status[b]				
Executive	18.7 (16.8–20.6)	34.8 (29.2–40.3)	28.8 (21–36.6)	40.0 (32.2–47.8)
Intermediate	19.9 (18.0–21.9)	27.6 (22.3–33.0)	31.6 (23.5–39.8)	24.1 (17.1–31.2)
Administration	28.9 (26.8–31.1)	24 (19.0–29.0)	23.3 (16.1–30.6)	24.6 (17.7–31.5)
Service, trade	15.8 (14.0–17.5)	7.1 (4.2–10.0)	7.5 (3.1–12.0)	6.7 (2.9–10.5)
Worker	12.8 (11.2–14.3)	5.8 (3.2–8.3)	7.3 (3.0–11.5)	4.5 (1.6–7.4)
Unemployed	3.9 (3.0–4.8)	0.8 (0.0–1.8)	1.5 (0.0–3.6)	0.2 (0.0–0.8)

Data are percentage (95% confidence interval) unless otherwise noted. Results are given after multiple imputation and are weighted to take into account the differences in survey design between gestational age groups; proportions are not exactly n/N because of the weighting.

ICSI, intracytoplasmic sperm injection; *IO*, induction of ovulation; *IUI*, intrauterine insemination; *IVF*, in vitro fertilization; *MAR*, medically assisted reproduction.

[a] MAR corresponds to the whole range of MAR techniques, that is, IO, IUI, IVF, and IVF-ICSI; [b] Defined as the highest occupational status between occupations of the mother and the father, or mother only if living alone.

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below the mean was lower among those born following IO or IUI than among those born after spontaneous conception, but all other results were nonsignificant after adjustment for sociodemographic factors and consistent with analyses of the full population. Results from the IVF/IVF-ICSI group were also consistent with the main results (Supplemental Table 4), with no differences seen in complete case analyses (Supplemental Tables 5 and 6).

Comment

Principal findings

In this prospective cohort study of preterm-born children followed-up at 5½ years of age, we found no evidence of an association between mode of conception and moderate to severe neurodevelopmental impairment following adjustment for sociodemographic factors, nor with cerebral palsy, sensory impairments, cognition, or developmental coordination disorders. Results were the same regardless of whether outcomes were analyzed as continuous scores or in binary categories representing potentially serious impairment. Sensitivity analyses using singletons and complete cases were also consistent.

Results in the context of what is known

Previous studies have identified differences in neurodevelopment related to mode of conception among children born preterm, particularly for cerebral palsy. One study that found an increased risk of cerebral palsy following IVF included children born between 1982 and 1995; however, evaluation was done at 2 years of age and results were only adjusted for the child's sex, year of birth, and maternal age[16]; moreover, IVF techniques have evolved since then.[12] Increased risk of cerebral palsy was identified for children born at <32 weeks' GA in a whole-population Australian study, but CIs were wide because few very preterm children were included.[33]

A different, prospective Australian cohort had similar findings, with an increased risk of moderate to severe neurodevelopmental impairment at 2 to 3 years of age for children born between

TABLE 2
Pregnancy and childbirth outcomes for 4349 children from the EPIPAGE-2 cohort surviving at 5½ years of age according to mode of conception, after multiple imputation

Outcomes	Spontaneous N children=3535	MAR[a] N children=814	IO or IUI N children=381	IVF or IVF-ICSI N children=433
Multiple pregnancy status				
Singleton	74.2 (72.2–76.1)	24.3 (20.5–28.1)	31.4 (25.1–37.7)	18.7 (14.2–23.3)
Twin	24.7 (22.8–26.6)	68.7 (64.6–72.9)	58.2 (51.5–64.9)	77.1 (72.1–82.0)
Triplet	1.1 (0.7–1.6)	6.7 (4.5–9.0)	9.9 (5.9–13.9)	4.2 (1.8–6.7)
Quadruplet	0.0	0.2 (0.0–0.4)	0.5 (0.1–0.9)	0.0
Antenatal steroids	75.6 (73.6–77.6)	85.5 (82.1–89.0)	79.4 (73.5–85.4)	90.3 (86.5–94.1)
Tocolysis	47.0 (44.8–49.2)	55.8 (51.2–60.4)	50.6 (43.7–57.5)	59.9 (53.7–66.1)
Spontaneous preterm delivery	51.7 (49.4–53.9)	44.7 (40.1–49.4)	49.8 (42.8–56.7)	40.8 (34.6–47.0)
Cephalic presentation	74.7 (72.8–76.6)	63.4 (59.0–67.8)	62.1 (55.5–68.6)	64.4 (58.5–70.4)
Cesarean delivery	58.6 (56.3–60.8)	60.8 (56.3–65.4)	62.3 (55.5–69.0)	59.7(51.3–68.1)
Maternity level III	61.9 (59.7–64.2)	66.8 (62.2–71.5)	63.6 (56.7–70.6)	69.3 (63.2–75.5)
Week of gestation, mean (95% confidence interval)	31.8 (31.7–31.9)	31.8 (31.6–31.9)	31.6 (31.4–31.9)	31.9 (31.6–32.1)
24–26 wk	4.1 (3.7–4.5)	5.4 (4.4–6.5)	6.0 (4.4–7.7)	5.0 (3.7–6.3)
27–31 wk	30.0 (28.4–31.5)	26.5 (23.6–29.5)	29.3 (24.6–34.0)	24.3 (20.5–28.1)
32–34 wk	65.9 (64.2–67.6)	68.0 (64.7–71.4)	64.7 (59.3–70.0)	70.7 (66.5–75.0)
Male sex	53.6 (51.3–55.8)	51.1 (46.5–55.7)	49.0 (42.2–55.8)	52.8 (46.6–59.1)
Small for gestational age[b]	32.8 (30.7–34.9)	36.7 (32.2–41.2)	41.5 (34.7–48.3)	32.9 (27.0–38.8)
Severe malformations	6.7 (5.6–7.8)	6.5 (4.3–8.7)	10.0 (5.9–14.2)	3.7 (1.7–5.7)

Data are percentage (95% confidence interval) unless otherwise noted. Results are given after multiple imputation and are weighted to take into account the differences in survey design between gestational age groups; proportions are not exactly n/N because of the weighting.

ICSI, intracytoplasmic sperm injection; *IO*, induction of ovulation; *IUI*, intrauterine insemination; *IVF*, in vitro fertilization; *MAR*, medically assisted reproduction.

[a] MAR corresponds to the whole range of MAR techniques, that is, IO, IUI, IVF, and IVF-ICSI; [b] Small-for-gestational-age was defined as birthweight <10th percentile for gestational age and sex on the basis of French intrauterine growth curves.[28]

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1998 and 2004 at 22 to 26 weeks' GA following MAR. However, in subgroup analysis this applied only to births following IVF or IVF-ICSI and not to those following IO or IUI. This study only adjusted for year of birth, maternal age, and parity.[21] A more recent prospective study evaluating neurodevelopment at 2 years of age in preterm infants born following MAR found a decreased risk of poor neurodevelopmental outcomes after adjusting for socioeconomic level[22]; similar results were found in a retrospective study adjusting for maternal education.[18] However, neither study accounted for missing data, and the results are thus difficult to interpret. Other studies were also restricted to complete-case analyses.[16,33] Not only did we use multiple imputation and perform sensitivity analyses on complete cases, but we also adjusted for multiple social factors, and found that any initially perceived differences in outcome following MAR disappeared following this adjustment.

Clinical implications

The finding that there are no differences in neurodevelopmental outcomes according to mode of conception in this prospectively collected French national cohort of very and moderately preterm children is highly likely to apply also in other countries. External validity may be limited because French perinatal care was less active than that of some other countries for neonates born extremely preterm (at <27 weeks' GA), but it was not dissimilar to that of other European countries[34]; furthermore, these children represented only approximately 5% of the births included in this study. Of greater concern might be that MAR techniques have changed: methods for both freezing embryos and the media in which they were subsequently cultured were different in 2011, and the transfer of several embryos was also more frequent and usually occurred at day 2 or 3.[10] However, evolution of practice has occurred internationally, not just within France, and longer-term follow-up necessarily requires that practices are

TABLE 3
Neurodevelopmental outcome measures for 4349 children from the EPIPAGE-2 cohort surviving at 5½ years according to mode of conception, after multiple imputation

	Spontaneous	MAR[a]		IO or IUI		IVF or IVF-ICSI	
Outcome	N=3535	N=814	*P* value[b]	N=381	*P* value[b]	N=433	*P* value[b]
Cerebral palsy	5.1 (4.0–6.2)	4.5 (2.4–6.6)	.62	6.3 (2.5–10.0)	.52	3.1 (0.9–5.2)	.16
Visual impairment							
Severe and moderate impairment[c]	1.3 (0.7–2.0)	0.9 (0.0–2.0)	.48	1.3 (0.0–3.3)	.94	0.5 (0.0–1.7)	.27
Hearing impairment							
Severe and moderate impairment[d]	1.1 (0.5–1.7)	1.5 (0.2–2.8)	.51	0.6 (0.0–2.0)	.42	2.2 (0.2–4.3)	.18
FSIQ[e]							
Mean (SD)	95.8 (15.7)	100.1 (15.5)	<.001	99.4 (15.5)	.011	100.6 (15.6)	<.001
<1 SD (<93)[f]	40.1 (37.4–42.8)	29.0 (24.6–33.5)	<.001	28.8 (22.0–35.7)	.008	29.1 (23.2–35.1)	.003
<2 SD (<79)[f]	13.4 (11.5–15.3)	8.6 (5.9–11.4)	.010	9.3 (5.2–13.4)	.13	8.1 (4.5–11.7)	.024
Neurodevelopmental impairment							
Severe and moderate impairment[g]	16.0 (14.0–17.9)	11.2 (8.0–14.4)	.020	12.1 (7.3–16.9)	.18	10.4 (6.3–14.5)	.036
Developmental coordination disorders[h]							
Total MABC-2 score, mean (SD)	10.2 (3.1)	10.5 (2.9)	.27	10.4 (3.1)	.52	10.5 (2.7)	.32
Total MABC-2 score <5th percentile[f]	5.9 (4.6–7.2)	4.4 (2.2–6.6)	.29	5.7 (1.9–9.4)	.90	3.4 (0.7–6.1)	.16

Data are percentage (95% confidence interval) unless otherwise noted. Results are given after multiple imputation and are weighted to take into account the differences in survey design between gestational age groups; proportions are not exactly n/N because of the weighting.

FSIQ, full-scale intelligence quotient; *ICSI*, intracytoplasmic sperm injection; *IO*, induction of ovulation; *IUI*, intrauterine insemination; *IVF*, in vitro fertilization; *MABC-2*, Movement Assessment Battery for Children, Second Edition (Henderson, 2007); *MAR*, medically assisted reproduction; *SD*, standard deviation.

[a] MAR corresponds to the whole range of MAR techniques, that is, IO, IUI, IVF, and IVF-ICSI; [b] Chi square test *P* value, estimated with the generalized estimating equations (GEE) approach to take into account correlation between twins or triplets, compared with spontaneous pregnancy; [c] Blindness or binocular corrected visual acuity <3.2/10; [d] Deafness, hearing loss >40 dB not corrected or partially corrected with hearing aid; [e] Full-scale intelligence quotient, measured by the Wechsler Preschool and Primary Scale of Intelligence—Fourth Edition[26]; [f] Cutoff of the distribution related to a reference group born at term[27]; [g] Severe or moderate cerebral palsy, severe or moderate sensory impairments, or FSIQ <2 SDs below the mean of a reference population; [h] Among children without cerebral palsy or severe or moderate sensory impairments, and with full-scale intelligence quotients ≥2 SDs below the mean of a reference population.

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TABLE 4
Association between mode of conception and neurodevelopmental outcome measures for 4349 children from the EPIPAGE-2 cohort surviving at 5½ years—multivariate analysis after multiple imputation

	MAR[a] (N children=814)		IO or IUI (N children=381)		IVF or IVF-ICSI (N children=433)	
	vs spontaneous conception (N children=3535)					
Outcome (Model)	OR or mean difference (95% CI)[b]	*P* value	OR or mean difference (95% CI)[b]	*P* value	OR or mean difference (95% CI)[b]	*P* value
Cerebral palsy						
Adjusted for GA and antenatal steroids	0.85 (0.59–1.24)	.41	0.89 (0.53–1.50)	.67	0.81 (0.49–1.35)	.42
Adjusted for GA, antenatal steroids, and sociodemographic variables[c]	1.00 (0.67–1.49)	.99	0.99 (0.59–1.69)	.99	1.00 (0.58–1.72)	.99
FSIQ[d]						
Mean difference (95% CI)						
Adjusted for GA and antenatal steroids	3.8 (2.4–5.3)	<.001	3.3 (1.3–5.3)	.002	4.3 (2.4–6.3)	<.001
Adjusted for GA, antenatal steroids, and sociodemographic variables[c]	−0.3 (−1.7 to 1.1)	.66	0.0 (−1.9 to 1.9)	.99	−0.6 (−2.5 to 1.3)	.52
<1 SD (<93)[e]						
Adjusted for GA and antenatal steroids	0.64 (0.53–0.77)	<.001	0.61 (0.46–0.80)	<.001	0.66 (0.52–0.85)	.001
Adjusted for GA, antenatal steroids, and sociodemographic variables[c]	0.99 (0.80–1.23)	.94	0.84 (0.62–1.15)	.28	1.15 (0.87–1.52)	.32
< 2 SD (<79)[e]						
Adjusted for GA and antenatal steroids	0.67 (0.51–0.88)	.004	0.69 (0.47–1.02)	.060	0.64 (0.44–0.94)	.023
Adjusted for GA, antenatal steroids, and sociodemographic variables[c]	1.14 (0.83–1.56)	.42	1.04 (0.69–1.57)	.86	1.26 (0.82–1.93)	.30
Severe and moderate neurodevelopmental impairment[f]						
Adjusted for GA and antenatal steroids	0.68 (0.53–0.88)	.003	0.72 (0.51–1.02)	.066	0.64 (0.45–0.91)	.013
Adjusted for GA, antenatal steroids, and sociodemographic variables[c]	1.09 (0.82–1.45)	.56	1.04 (0.72–1.51)	.83	1.14 (0.77–1.68)	.51
Developmental coordination disorders[g]						
Total MABC-2 score, mean difference (95% CI)						
Adjusted for GA and antenatal steroids	0.2 (−0.1 to 0.5)	.28	0.1 (−0.3 to 0.5)	.67	0.2 (−0.2 to 0.6)	.25
Adjusted for GA, antenatal steroids, and sociodemographic variables[c]	0.1 (−0.3 to 0.4)	.74	0.0 (−0.4 to 0.5)	.92	0.1 (−0.3 to 0.5)	.69
Total MABC-2 score <fifth percentile[e]						
Adjusted for GA and antenatal steroids	0.76 (0.51–1.11)	.16	0.77 (0.45–1.31)	.34	0.74 (0.43–1.28)	.28
Adjusted for GA, antenatal steroids, and sociodemographic variables[c]	0.75 (0.50–1.12)	.16	0.77 (0.45–1.31)	.33	0.73 (0.41–1.29)	.28

CI, confidence interval; *FSIQ*, full-scale intelligence quotient; *GA*, gestational age; *ICSI*, intracytoplasmic sperm injection; *IO*, induction of ovulation; *IUI*, intrauterine insemination; *IVF*, in vitro fertilization; *MABC-2*, Movement Assessment Battery for Children, Second Edition (Henderson, 2007); *MAR*, medically assisted reproduction; *OR*, odds ratio; *SD*, standard deviation.

[a] MAR corresponds to the whole range of MAR techniques, that is, IO, IUI, IVF, and IVF-ICSI; [b] The reported measures of association are odds ratios, except for FSIQ and total MABC-2 scores, where mean differences are reported. The generalized estimating equations approach was used to take into account correlation between twins or triplets; [c] Sociodemographic factors adjusted for are: maternal age, parity, education level, employment status, living with a partner, smoking during pregnancy, country of birth, and parents' socioeconomic status; [d] Full-scale intelligence quotient, measured by the Wechsler Preschool and Primary Scale of Intelligence—Fourth Edition[26]; [e] Cutoff of the distribution related to a reference group born at term[27]; [f] Severe or moderate cerebral palsy, severe or moderate sensory impairment, or FSIQ <2 SDs below the mean of a reference population; [g] Among children without cerebral palsy or severe or moderate sensory impairment, and with FSIQ ≥2 SDs below the mean of a reference population.

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from the past, thus implying that they are likely to have evolved in the interim period. Consequently, this study should be reassuring for health professionals and parents or parents-to-be of children born preterm following MAR because it indicates that any developmental consequences arise from preterm birth rather than the mode of conception itself conveying an additional risk.

Research implications

Although EPIPAGE-2 contains a wealth of follow-up and social data, information was limited about the MAR techniques. We did not have details about which drugs were used and at what dose, or whether embryos were transferred fresh or frozen, nor could we identify children born from donated gametes. This leaves questions about the impact of more specific fertility treatments for future research.

Strengths and limitations

This study evaluated multiple dimensions of longer-term neurodevelopment among children born preterm according to the mode of conception. Using a large, prospectively collected national cohort with comprehensive data covering a range of medical and sociodemographic characteristics[24,25] allowed us to study several neurodevelopmental outcomes while taking into consideration important confounding factors with sufficient power to detect potential differences, particularly for the most frequent outcomes (cognitive impairment, developmental coordination disorder, and cerebral palsy). The quality of the used sociodemographic information is a further strength: most previous studies had only medical data with minimal additional information, and given that the social environment is a major predictor of child development, residual confounding may have been an issue. The main difficulty in prospective cohort studies is loss to follow-up.[35] Data we had available covered pregnancy, the neonatal hospitalization, and subsequent course of the children, thus allowing us to use these data in imputation models, thereby increasing the likelihood of the "missing at random" assumption being met.[32] This is important because missing data may have impact in ways that are difficult to determine.[35] We were further reassured by the very similar results found in analyses using complete cases. We were also able to examine the implication of broader MAR techniques both together and separated into ART and non-ART techniques, although more detailed information about specific techniques was not available; previous studies in the preterm population have predominantly focused on children born either after IVF/IVF-ICSI[16,36] or after all types of MAR combined.[18,21,22] Only 1 other study separated ART and non-ART techniques, but it only examined the relationship with cerebral palsy and was restricted in the sociodemographic variables available for inclusion because the data were obtained from national registers.[23] Our study was also limited by its restriction to preterm-born children; we are therefore only able to state that there was no increased risk of neurodevelopmental impairment according to mode of conception in this population, but it is also important to remember that there are increased risks of multiple pregnancy and preterm birth with the use of MAR.[10,12]

Conclusion

In summary, we assessed neurodevelopmental outcomes at $5^1/_2$ years of age for children born preterm following MAR, and after adjusting for social characteristics, found no differences from children born following spontaneously conceived pregnancies. These are important insights for obstetricians, pediatricians, and other healthcare professionals working with women and their families. Our study provides further evidence for health professionals to reassure parents or parents-to-be when a child conceived from MAR is born preterm. ■

Acknowledgments

The authors wish to thank everyone involved in the EPIPAGE-2 Study Groups.

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All the collaborators of the EPIPAGE2 Obstetric writing group have no conflict of interest or compensation in relation with this article to disclose. All of them consented to such acknowledgment.

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References

1. Zegers-Hochschild F, Adamson GD, Dyer S, et al. The international glossary on infertility and fertility care, 2017. Hum Reprod 2017;32:1786–801.

2. Oakley L, Doyle P, Maconochie N. Lifetime prevalence of infertility and infertility treatment in the UK: results from a population-based survey of reproduction. Hum Reprod 2008;23:447–50.

3. Schmidt L. Social and psychological consequences of infertility and assisted reproduction - what are the research priorities? Hum Fertil (Camb) 2009;12:14–20.

4. Peterson BD, Pirritano M, Christensen U, Boivin J, Block J, Schmidt L. The longitudinal impact of partner coping in couples following 5 years of unsuccessful fertility treatments. Hum Reprod 2009;24:1656–64.

5. Volgsten H, Skoog Svanberg A, Ekselius L, Lundkvist O, Sundström Poromaa I. Prevalence of psychiatric disorders in infertile women and men undergoing in vitro fertilization treatment. Hum Reprod 2008;23:2056–63.

6. Chachamovich JR, Chachamovich E, Ezer H, Fleck MP, Knauth D, Passos EP. Investigating quality of life and health-related quality of life in infertility: a systematic review. J Psychosom Obstet Gynaecol 2010;31:101–10.

7. Facchin F, Somigliana E, Busnelli A, Catavorello A, Barbara G, Vercellini P. Infertility-related distress and female sexual function during assisted reproduction. Hum Reprod 2019;34:1065–73.

8. Gabr AA, Omran EF, Abdallah AA, et al. Prevalence of sexual dysfunction in infertile

versus fertile couples. Eur J Obstet Gynecol Reprod Biol 2017;217:38–43.

9. Goisis A, Håberg SE, Hanevik HI, Magnus MC, Kravdal Ø. The demographics of assisted reproductive technology births in a Nordic country. Hum Reprod 2020;35:1441–50.

10. De Geyter C, Calhaz-Jorge C, Kupka MS, et al. ART in Europe, 2015: results generated from European registries by ESHRE. Hum Reprod Open 2020;2020:hoz038.

11. Mani S, Ghosh J, Coutifaris C, Sapienza C, Mainigi M. Epigenetic changes and assisted reproductive technologies. Epigenetics 2020;15:12–25.

12. Berntsen S, Söderström-Anttila V, Wennerholm UB, et al. The health of children conceived by ART: 'the chicken or the egg?'. Hum Reprod Update 2019;25:137–58.

13. Wolke D, Johnson S, Mendonça M. The life course consequences of very preterm birth. Annu Rev Dev Psychol 2019;1:69–92.

14. Doyle LW, Spittle A, Anderson PJ, Cheong JLY. School-aged neurodevelopmental outcomes for children born extremely preterm. Arch Dis Child 2021;106:834–8.

15. Morgan AS, Mendonça M, Thiele N, David AL. Management and outcomes of extreme preterm birth. BMJ (Clin Res Ed) 2022;376:e055924.

16. Strömberg B, Dahlquist G, Ericson A, Finnström O, Köster M, Stjernqvist K. Neurological sequelae in children born after in-vitro fertilisation: a population-based study. Lancet 2002;359:461–5.

17. Hashimoto K, Ogawa K, Horikawa R, et al. Gross motor function and general development of babies born after assisted reproductive technology. J Obstet Gynaecol Res 2016;42:266–72.

18. Roychoudhury S, Lodha A, Synnes A, et al. Neurodevelopmental outcomes of preterm infants conceived by assisted reproductive technology. Am J Obstet Gynecol 2021;225:276.e1–9.

19. Balayla J, Sheehy O, Fraser WD, et al. Neurodevelopmental outcomes after assisted reproductive technologies. Obstet Gynecol 2017;129:265–72.

20. Torchin H, Morgan AS, Ancel PY. International comparisons of neurodevelopmental outcomes in infants born very preterm. Semin Fetal Neonatal Med 2020;25:101109.

21. Abdel-Latif ME, Bajuk B, Ward M, Oei JL, Badawi N. NSW and ACT Neonatal Intensive Care Units Audit Group. Neurodevelopmental outcomes of extremely premature infants conceived after assisted conception: a population based cohort study. Arch Dis Child Fetal Neonatal Ed 2013;98:F205–11.

22. Molines L, Nusinovici S, Moreau M, et al. Impact of mode of conception on neonatal and neurodevelopmental outcomes in preterm infants. Hum Reprod 2019;34:356–64.

23. Hvidtjørn D, Grove J, Schendel D, et al. Multiplicity and early gestational age contribute to an increased risk of cerebral palsy from assisted conception: a population-based cohort study. Hum Reprod 2010;25:2115–23.

24. Ancel PY, Goffinet F; EPIPAGE 2 Writing Group. EPIPAGE 2: a preterm birth cohort in France in 2011. BMC Pediatr 2014;14:97.

25. Lorthe E, Benhammou V, Marchand-Martin L, et al. Cohort profile: the Etude Epidemiologique sur les Petits Ages Gestationnels-2 (EPIPAGE-2) preterm birth cohort. Int J Epidemiol 2021;50:1428–1429m.

26. Wechsler D. Pearson clinical & talent assessment. WPPSI-IV — échelle d'intelligence de Wechsler pour enfants. 4ème édition. Published online; 2014. Available at: https://nam11.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.pearsonclinical.fr%2Fwppsi-iv&data=05%7C01%7Co.pyne%40elsevier.com%7Caa0e7f2049e64760293908da60bcef05%7C9274ee3f94254109a27f9fb15c10675d%7C0%7C0%7C637928661831652672%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C3000%7C%7C%7C&sdata=EDWl9TVmmOovyalAkd9kBjaLo49FYY2tEor5jkJqlcM%3D&reserved=0. Accessed June 23, 2022

27. Pierrat V, Marchand-Martin L, Marret S, et al. Neurodevelopmental outcomes at age 5 among children born preterm: EPIPAGE-2 cohort study. BMJ 2021;373:n741.

28. Ego A, Prunet C, Lebreton E, et al. [Customized and non-customized French intrauterine growth curves. I - methodology]. J Gynecol Obstet Biol Reprod (Paris) 2016;45:155–64.

29. Rubin DB. Multiple Imputation for non response in surveys, 1st ed. Chichester: John Wiley & Sons, Inc; 1987.

30. R Core Team. R: A language and environment for statistical computing. Version 4.0.4 (2021-02-15) – "Lost Library Book". R Foundation for Statistical Computing: Vienna, Austria. 2021 Available at: https://nam11.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.r-project.org%2F&data=05%7C01%7Co.pyne%40elsevier.com%7Caa0e7f2049e64760293908da60bcef05%7C9274ee3f94254109a27f9fb15c10675d%7C0%7C0%7C637928661831652672%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C3000%7C%7C%7C&sdata=11FP%2BpyTa8yijpTnPsByB01GXlPYj97wdVwJhvL5k%2BE%3D&reserved=0.

31. Højsgaard S, Halekoh U, Yan J. The R package geepack for Generalized Estimating Equations. J Stat Softw 2005;15:1–11.

32. van Buuren S, Groothuis-Oudshoorn K. mice: multivariate Imputation by Chained Equations in R. J Stat Soft 2011;45:1–67.

33. Goldsmith S, Mcintyre S, Badawi N, Hansen M. Cerebral palsy after assisted reproductive technology: a cohort study. Dev Med Child Neurol 2018;60:73–80.

34. Edstedt Bonamy AK, Zeitlin J, Piedvache A, et al. Wide variation in severe neonatal morbidity among very preterm infants in European regions. Arch Dis Child Fetal Neonatal Ed 2019;104:F36–45.

35. Wolke D, Söhne B, Ohrt B, Riegel K. Follow-up of preterm children: important to document dropouts. Lancet 1995;345:447.

36. Hvidtjørn D, Grove J, Schendel DE, et al. Cerebral palsy among children born after in vitro fertilization: the role of preterm delivery—a population-based, cohort study. Pediatrics 2006;118:475–82.

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Received Feb. 10, 2022; revised May 20, 2022; accepted May 28, 2022.

The authors report no conflict of interest.

This project has been funded with support from:

1. The French Institute of Public Health Research/Institute of Public Health and its partners: the French Health Ministry, the National Institute of Health and Medical Research (INSERM), the National Institute of Cancer, and the National Solidarity Fund for Autonomy (CNSA).

2. The National Research Agency through the French EQUIPEX program of investments in the future (reference ANR-11-EQPX-0038 and ANR-19-COHO-001).

3. The PremUp Foundation.

4. Fondation de France (reference 11779).

5. Fondation pour la Recherche Médicale (SPF20160936356 — A.S.M.).

6. Programme Hospitalier de Recherche Clinique Epinutri (DGOS13-040).

7. Ministère de l'Enseignement Supérieur, de la Recherche et de l'Innovation (G13129KK).

8. APICIL Foundation (R20065KK).

The findings of this study have been presented at the following meetings:

■ As an oral presentation at the 2021 conference of the Journées Francophones de Recherche en Néonatologie for the French Neonatal Society, Paris, France, December 9—10, 2021;

■ As a poster at the 2021 annual conference of the British Association of Perinatal Medicine, held virtually, October 4—5, 2021;

■ As an oral presentation at the 8th congress of the European Academy of Paediatric Societies - EAPS 2020, held virtually, October 16—19, 2020.

Data availability: The data are, in principle, accessible to all research teams, public, French, or foreign, subject to authorization by the cohort Data Access Committee.

The new law for modernization of the French Public Health System voted in 2016 now provides a legal framework for access to and reuse of already collected cohort data by complying with 'Reference Methodology MR-004.' Therefore, only nonnominative data defined as having a low reidentification risk are accessible. Moreover, general information on research activities in the institution must be provided to the persons concerned (posting on the premises, entry in the welcome booklet, etc.).

To this general information, individual patient information must be delivered for each project in which the patient is involved or for which the patient data will be treated.

As a consequence, each data access request must be submitted to the EPIPAGE-2 Data Access Committee (DAC) that evaluates the research projects on the basis of the following criteria: (1) methodological strengths and weaknesses (feasibility, choice of methods to achieve the objectives), (2) absence of overlap with other ongoing projects, in which case discussions with the different teams are organized, and (3) relevance of the requested data for the project and respect for confidentiality.

The study protocol, the data access charter, and the data access procedure can be found on the EPIPAGE-2 website (https://epipage2.inserm.fr/index.php/fr/cote-recherche/235-acces-aux-donnees-et-questionnaires). Questionnaires and data catalogs are available on https://pandora-epipage2.inserm.fr/public/.

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SUPPLEMENTAL TABLE 1

Type of variables, model used to predict missing data, and percentages of values missing for each variable included in the imputation model (N = 4349 live children at 5.5 years)

Variable	Type of variable	Model used to predict missing data	Percentage of missing values among survivors at 5.5 y
Perinatal characteristics			
Mode of conception (spontaneous, IO, IUI, IVF, IVF-ICSI)	Categorical (5 categories)	No missing data	0%
GA by week	Categorical (11 categories)	No missing data	0%
Birth country	Categorical (5 categories)	Multinomial regression	1%
Maternal age at delivery	Continuous	No missing data	0%
Primiparity	Binary	Logistic regression	1%
Parents' socioeconomic status[a]	Categorical (6 categories)	Multinomial regression	5%
Maternal level of education	Categorical (4 categories)	Multinomial regression	7%
Smoking during pregnancy	Binary	Logistic regression	3%
Occupational activity during pregnancy	Binary	Logistic regression	6%
Living with partner at delivery	Binary	Logistic regression	5%
Antenatal steroids	Binary	Logistic regression	2%
Tocolysis	Binary	Logistic regression	<1%
Pregnancy type (singleton or twins)	Categorical (4 categories)	Multinomial regression	0%
Spontaneous preterm delivery	Binary	Logistic regression	3%
Cephalic presentation	Binary	Logistic regression	3%
Maternity level	Binary	No missing data	0%
Caesarean delivery	Binary	Logistic regression	1%
Sex	Binary	No missing data	0%
SGA[b]	Binary	Logistic regression	<1%
Severe congenital malformations	Binary	No missing data	0%
Surfactant	Binary	Logistic regression	1%
Severe cerebral lesions	Binary	Logistic regression	1%
Severe bronchopulmonary dysplasia	Binary	Logistic regression	3%
Severe necrotizing enterocolitis	Binary	Logistic regression	2%
Suspected early-onset neonatal sepsis	Binary	Logistic regression	4%
Late-onset neonatal sepsis	Binary	Logistic regression	1%
At 2 y			
Cerebral palsy	Categorical (5 categories)	Multinomial regression	19%
Hearing impairment	Categorical (3 categories)	Multinomial regression	21%
Visual impairment	Categorical (3 categories)	Multinomial regression	23%
ASQ communication score	Continuous	Predictive mean matching	18%
ASQ gross motor score	Continuous	Predictive mean matching	20%
ASQ fine motor score	Continuous	Predictive mean matching	21%
ASQ problem-solving score	Continuous	Predictive mean matching	21%
ASQ personal-social score	Continuous	Predictive mean matching	21%

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SUPPLEMENTAL TABLE 1

Type of variables, model used to predict missing data, and percentages of values missing for each variable included in the imputation model (N = 4349 live children at 5.5 years) *(continued)*

Variable	Type of variable	Model used to predict missing data	Percentage of missing values among survivors at 5.5 y
At 5 y			
Support at school or special schooling	Categorical (3 categories)	Multinomial regression	33%
Cerebral palsy	Categorical (5 categories)	Multinomial regression	31%
Hearing impairment	Categorical (4 categories)	Multinomial regression	32%
Visual impairment	Categorical (4 categories)	Multinomial regression	40%
WPPSI-IV Verbal Comprehension Index score	Continuous	Predictive mean matching	40%
WPPSI-IV Visual-Spatial Index score	Continuous	Predictive mean matching	40%
WPPSI-IV Fluid Reasoning Index score	Continuous	Predictive mean matching	40%
WPPSI-IV Working Memory Index score	Continuous	Predictive mean matching	40%
WPPSI-IV Processing Speed Index score	Continuous	Predictive mean matching	40%
WPPSI-IV Full Scale IQ score	Continuous	Predictive mean matching	40%
MABC-2 total score	Continuous	Predictive mean matching	42%
SDQ total score	Continuous	Predictive mean matching	40%

All variables were included as a predictor in all imputation models.

ASQ, Ages and Stages Questionnaire (Squire, 2009); *GA*, gestational age; *ICSI*, intracytoplasmic sperm injection; *IO*, induction of ovulation; *MABC-2*, Movement Assessment Battery for Children-Second Edition (Henderson, 2007); *SDQ*, Strengths and Difficulties Questionnaire (Goodman, 1997); *MAR*, medically assisted reproduction; *IUI*, intrauterine insemination; *IVF*, in vitro fertilization; *SGA*, small for gestational age; *WPPSI*, Wechsler Preschool and Primary Scale of Intelligence-Fourth Edition (Wechsler, 2014).

[a] Defined as the highest occupational status among occupations of the mother and the father or mother only if living alone; [b] SGA was defined as a birthweight of <10th percentile for GA and sex based on the French intrauterine growth curves.[28]

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SUPPLEMENTAL TABLE 2

Comparison of children participating and nonparticipating in follow-up (N = 4349 live children at 5.5 years)

Variable	Participating children at 5.5 years n=3031		Non-participating children at 5.5 years n=1318		Chi-squared *P* value
Mode of conception					
Spontaneous	2390/3031	78.1	1145/1318	86.7	<.001
MAR[a]	641/3031	21.9	173/1318	13.3	
IO or IUI	299/3031	9.6	82/1318	6.0	
IVF or IVF-ICSI	342/3031	12.3	91/1318	7.3	
Maternal characteristics at birth					
Maternal age, mean (SD)	3031	30.5 (5.5)	1318	28.9 (6.0)	<.001
Primiparous	1699/3004	56.5	652/1298	51.7	.031
Born in France	2477/3025	85.0	891/1284	71.2	<.001
Smoked during pregnancy	564/2949	17.9	344/1285	25.2	<.001
Maternal level of education					
Less than high school	835/2938	27.1	486/1098	42.4	<.001
High school	605/2938	20.4	268/1098	24.6	
1–2 y of graduate studies	622/2938	21.7	156/1098	13.9	
≥3 y of graduate studies	876/2938	30.8	188/1098	19.1	
Occupational activity during pregnancy	1976/2841	71.3	640/1236	55.7	<.001
Cohabiting with partner at delivery	2686/2884	94.0	1067/1246	84.6	<.001
Parents' socioeconomic status[b]					
Executive	742/2921	26.3	168/1215	15.3	<.001
Intermediate	696/2921	25.0	176/1215	15.6	
Administration	761/2921	25.6	375/1215	31.9	
Service, trade	360/2921	11.9	228/1215	17.6	
Worker	308/2921	9.4	184/1215	13.8	
Unemployed	54/2921	1.7	84/1215	5.8	
Obstetrical and neonatal factors					
Multiple pregnancy status					
Singleton	1967/3031	62.7	916/1318	68.6	<.001
Twins	991/3031	34.8	372/1318	29.6	
Triplets	68/3031	2.4	30/1318	1.8	
Quadruplets	5/3031	0.1	0/1318	0.0	
Antenatal steroids	2466/2986	78.6	1024/1295	75.1	.068
Tocolysis	1595/3012	48.7	700/1311	48.8	.98
Spontaneous preterm delivery	1422/2916	48.9	684/1285	53.4	.046
Cephalic presentation	1975/2937	71.6	887/1271	74.4	.313
Cesarean delivery	1960/3019	60.8	782/1306	55.7	.019
Maternity level III	2373/3031	64.7	974/1318	59.0	<.001
GA at birth (wk), mean (SD)	3031	31.7 (2.4)	1318	32.0 (2.3)	

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SUPPLEMENTAL TABLE 2

Comparison of children participating and nonparticipating in follow-up (N = 4349 live children at 5.5 years) *(continued)*

Variable	Participating children at 5.5 years n=3031		Non-participating children at 5.5 years n=1318		Chi-squared *P* value
24–26	375/3031	4.6	159/1318	4.0	<.001
27–31	1900/3031	31.1	759/1318	25.7	
32–34	756/3031	64.3	400/1318	70.3	
Male gender	1605/3031	54.6	683/1318	50.1	.040
SGA[c]	1053/3030	34.3	437/1318	32.0	.31
Severe malformations	223/3031	7.3	92/1318	5.4	.069

Data are presented as number of events/number in groups or percentages, unless otherwise indicated. For observed data, denominators vary according to the number of missing data for each variable. Results are weighted to consider the differences in survey design among GA groups. Proportions are not exactly number/total number because of weighting.

GA, gestational age; *ICSI*, intracytoplasmic sperm injection; *IO*, induction of ovulation; *IUI*, intrauterine insemination; *IVF*, in vitro fertilization; *MAR*, medically assisted reproduction; *SD*, standard deviation; *SGA*, small for gestational age.

[a] MAR corresponds to the whole range of MAR techniques (ie, IO, IUI, IVF, and IVF-ICSI); [b] Defined as the highest occupational status among occupations of the mother and the father or mother only if living alone; [c] SGA was defined as a birthweight of <10th percentile for GA and sex based on French intrauterine growth curves.[28]

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SUPPLEMENTAL TABLE 3
Survival at 5.5 years according to mode of conception (N = 4907 live births included)

Variable	Spontaneous		MAR[a]		*P* value[b]	IO or IUI		*P* value[b]	IVF or IVF-ICSI		*P* value[b]
	No. of children = 4004		No. of children = 903			No. of children = 421			No. of children = 482		
Survival					.025			.15			.60
Deaths in delivery room	124	1.4	18	1.0		8	0.8		10	1.2	
Neonatal deaths	321	4.0	70	3.4		31	3.7		39	3.2	
Deaths after discharge	24	0.6	1	0.1		1	0.1		0	0.0	
Survival at 5.5 years	3535	94.0	814	95.5		381	95.4		433	95.6	

Data are presented as number of events and percentages. Denominators vary according to the number of missing data for each variable. Results are weighted to consider the differences in survey design among gestational age groups. Proportions are not exactly number/total number because of weighting.

ICSI, intracytoplasmic sperm injection; *IO*, induction of ovulation; *IUI*, intrauterine insemination; *IVF*, in vitro fertilization; *MAR*, medically assisted reproduction.

[a] MAR corresponds to the whole range of MAR techniques (ie, OI, IUI, IVF, and IVF-ICSI); [b] Chi-squared test *P* value, estimated with generalized estimating equations approach to consider the correlation between twins and triplets, compared to spontaneous pregnancy.

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SUPPLEMENTAL TABLE 4

Association between mode of conception and neurodevelopmental outcome measures at 5.5 years, multivariate analysis after multiple imputation, among singleton pregnancies

Variable	MAR[a] (no. of children = 231) vs Spontaneous conception (no. of children = 2652)		IO or IUI (no. of children = 123) vs Spontaneous conception (no. of children = 2652)		IVF or IVF-ICSI (no. of children = 108) vs Spontaneous conception (no. of children = 2652)	
	OR or MD (95% CI)[b]	*P* value	OR or MD (95% CI)[b]	*P* value	OR or MD (95% CI)[b]	*P* value
Cerebral palsy						
Adjusted for GA and antenatal steroids	1.04 (0.58–1.86)	.90	1.04 (0.46–2.32)	.93	1.02 (0.45–2.33)	.95
Adjusted for GA, antenatal steroids, and sociodemographic variables[c]	1.26 (0.69–2.31)	.45	1.24 (0.55–2.79)	.61	1.27 (0.54–2.99)	.58
Full Scale IQ[d]						
MD (95% CI)						
Adjusted for GA and antenatal steroids	4.6 (2.3–6.9)	<.001	3.6 (0.6–6.6)	.020	5.8 (2.4–9.2)	<.001
Adjusted for GA, antenatal steroids, and sociodemographic variables[c]	1.2 (−1.0 to 3.3)	.29	0.9 (−1.9 to 3.7)	.53	1.5 (−1.7 to 4.7)	.36
<1 SD (<93)[e]						
Adjusted for GA and antenatal steroids	0.52 (0.38–0.73)	<.001	0.48 (0.31–0.75)	.001	0.57 (0.36–0.92)	.022
Adjusted for GA, antenatal steroids, and sociodemographic variables[c]	0.72 (0.49–1.04)	.079	0.59 (0.36–0.96)	.035	0.89 (0.53–1.51)	.67
<2 SD (<79)[e]						
Adjusted for GA and antenatal steroids	0.64 (0.40–1.03)	.068	0.67 (0.36–1.24)	.20	0.61 (0.30–1.24)	.17
Adjusted for GA, antenatal steroids, and sociodemographic variables[c]	0.99 (0.59–1.66)	.97	0.92 (0.47–1.79)	.81	1.08 (0.50–2.32)	.85
Severe and moderate neurodevelopmental impairment[f]						
Adjusted for GA and antenatal steroids	0.63 (0.40–1.00)	.05	0.64 (0.36–1.17)	.15	0.61 (0.31–1.19)	.14
Adjusted for GA, antenatal steroids, and sociodemographic variables[c]	0.93 (0.56–1.53)	.77	0.86 (0.46–1.62)	.65	1.01 (0.49–2.06)	.98
Developmental coordination disorders[g]						
Total MABC-2 score, MD (95% CI)						
Adjusted for GA and antenatal steroids	0.2 (−0.4 to 0.7)	.53	0.2 (−0.6 to 0.9)	.67	0.2 (−0.6 to 0.9)	.63
Adjusted for GA, antenatal steroids, and sociodemographic variables[c]	0.1 (−0.5 to 0.6)	.79	0.1 (−0.6 to 0.8)	.81	0.1 (−0.7 to 0.8)	.89
Total MABC-2 score<5th percentile[e]						
Adjusted for GA and antenatal steroids	0.75 (0.39–1.43)	.39	0.83 (0.36–1.91)	.66	0.66 (0.24–1.78)	.41
Adjusted for GA, antenatal steroids, and sociodemographic variables[c]	0.76 (0.39–1.46)	.40	0.84 (0.36–1.94)	.68	0.66 (0.24–1.79)	.41

CI, confidence interval; *GA*, gestational age; *ICSI*, intracytoplasmic sperm injection; *IQ*, intelligence quotient; *IUI*, intrauterine insemination; *IVF*, in vitro fertilization; *MABC-2*, Movement Assessment Battery for Children-Second Edition (Henderson, 2007); *MAR*, medically assisted reproduction; *MD*, mean difference; *OI*, ovulation induction; *OR*, odds ratio; *SD*, standard deviation.

[a] MAR corresponds to the whole range of MAR techniques (ie, OI, IUI, IVF, and IVF-ICSI); [b] The reported measures of association are OR, except for Full Scale IQ and total MABC-2 score where MDs are reported; [c] Sociodemographic factors adjusted for were maternal age, parity, education level, employment status, living with a partner, smoking during pregnancy, country of birth, and parents' socioeconomic status; [d] Full Scale IQ, measured using the Wechsler Preschool and Primary Scale of Intelligence-Fourth Edition[26]; [e] Cutoff of the distribution related to a reference group born at term[27]; [f] Severe or moderate cerebral palsy, severe or moderate sensory disabilities, or Full Scale IQ <2 SDs below the mean of a reference population; [g] Among children without cerebral palsy, without severe or moderate sensory disabilities, and with Full Scale IQ ≥2 SDs below the mean of a reference population.

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SUPPLEMENTAL TABLE 5
Neurodevelopmental outcome measures at 5.5 years according to mode of conception (complete case analysis)

Variables	Spontaneous		MAR[a]		*P* value[b]	IO or IUI		*P* value[b]	IVF or IVF-ICSI		*P* value[b]
Cerebral palsy	116/2368	3.4	32/638	4.0	.54	15/298	5.9	.12	17/340	2.6	.43
Visual impairment											
Severe and moderate impairment[c]	12/2049	0.5	3/570	0.6	.81	2/259	1.2	.34	1/311	0.1	.27
Hearing impairment											
Severe and moderate impairment[d]	18/2312	0.6	9/627	1.6	.10	2/292	0.3	.24	7/335	2.6	.014
Full Scale IQ[e]											
Mean (SD)	2037	97.9 (14.4)	552	101.2 (14.9)	<.001	251	100.7 (14.6)	.051	301	101.7 (15.1)	.003
<1 SD (<93)[f]	757/2037	34.0	168/552	25.6	.029	72/251	24.5	.026	96/301	26.4	.048
<2 SD (<79)[f]	225/2037	8.7	55/552	6.6	.14	27/251	6.9	.33	28/301	6.4	.22
Neurodevelopmental impairment											
Severe and moderate impairment[g]	283/2059	10.5	70/556	9.2	.41	36/225	10.1	.81	34/301	8.4	.36
Developmental coordination disorders[h]											
Total MABC-2 score, mean (SD)	1713	10.3 (3.0)	470	10.5 (2.8)	.34	213	10.4 (3.2)	.72	257	10.6 (2.5)	.27
Total MABC-2 score<5th percentile[f]	134/1713	5.1	28/470	3.7	.25	14/213	5.8	.74	14/257	2.1	.005

Data are presented as number of events/number in groups or percentages, unless otherwise indicated. Denominators vary according to the number of missing data for each variable. Results are weighted to consider the differences in survey design among gestational age groups. Proportions are not exactly number/total number because of the weighting.

ICSI, intracytoplasmic sperm injection; *IO*, induction of ovulation; *IQ*, intelligence quotient; *IUI*, intrauterine insemination; *IVF*, in vitro fertilization; *MABC-2*, Movement Assessment Battery for Children-Second Edition (Henderson, 2007); *MAR*, medically assisted reproduction; *SD*, standard deviation.

[a] MAR corresponds to the whole range of MAR techniques (ie IO, IUI, IVF, and IVF-ICSI); [b] Chi-squared test *P* value, estimated with generalized estimating equations approach to consider the correlation between twins and triplets, compared to spontaneous pregnancy; [c] Blindness or binocular corrected visual acuity of <3.2/10; [d] Deafness, hearing loss of >40 dB not corrected or partially corrected with hearing aid; [e] Full Scale IQ, measured by the Wechsler Preschool and Primary Scale of Intelligence-Fourth Edition[26]; [f] Cutoff of the distribution related to a reference group born at term[27]; [g] Severe or moderate cerebral palsy, severe or moderate sensory impairment, or Full Scale IQ quotient <2 SDs below the mean of a reference group; [h] Among children without cerebral palsy, without severe or moderate sensory impairment, and with Full Scale IQ ≥2 SDs below the mean of a reference group.

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SUPPLEMENTAL TABLE 6

Association between mode of conception and neurodevelopmental outcome measures at 5.5 years (multivariate complete case analysis)

Variable	MAR[a] vs Spontaneous conception		IO or IUI vs Spontaneous conception		IVF or IVF-ICSI vs Spontaneous conception	
	OR or MD (95% CI)[b]	*P* value	OR or MD (95% CI)[b]	*P* value	OR or MD (95% CI)[b]	*P* value
Cerebral palsy						
Adjusted for GA and antenatal steroids	1.03 (0.67–1.58)	.90	0.95 (0.52–1.72)	.86	1.11 (0.64–1.93)	.71
Adjusted for GA, antenatal steroids, and sociodemographic variables[c]	1.17 (0.67–2.03)	.58	0.90 (0.43–1.92)	.79	1.48 (0.75–2.89)	.26
Full Scale IQ,[d] MD (95% CI)						
Adjusted for GA and antenatal steroids	2.6 (1.0–4.3)	.002	2.2 (−0.1 to 4.4)	.057	3.0 (0.8–5.2)	.007
Adjusted for GA, antenatal steroids, and sociodemographic variables[c]	0.1 (−1.5 to 1.8)	.86	0.9 (−1.2 to 3.0)	.40	−0.6 (−2.9 to 1.7)	.63
<1 SD (<93)[e]						
Adjusted for GA and antenatal steroids	0.72 (0.57–0.90)	.004	0.63 (0.45–0.88)	.007	0.79 (0.60–1.06)	.110
Adjusted for GA, antenatal steroids, and sociodemographic variables[c]	0.99 (0.74–1.32)	.95	0.76 (0.51–1.13)	.18	1.26 (0.88–1.80)	.20
<2 SD (<79)[e]						
Adjusted for GA and antenatal steroids	0.91 (0.64–1.30)	.61	0.94 (0.59–1.51)	.80	0.88 (0.54–1.45)	.62
Adjusted for GA, antenatal steroids, and sociodemographic variables[c]	1.29 (0.82–2.01)	.27	1.04 (0.59–1.85)	.88	1.62 (0.88–2.96)	.12
Severe and moderate neurodevelopmental impairment[f]						
Adjusted for GA and antenatal steroids	0.95 (0.69–1.29)	.73	1.01 (0.68–1.51)	.95	0.88 (0.57–1.37)	.57
Adjusted for GA, antenatal steroids, and sociodemographic variables[c]	1.33 (0.90–1.96)	.15	1.19 (0.73–1.93)	.49	1.51 (0.89–2.54)	.12
Developmental coordination disorders[g]						
Total MABC-2 score, MD (95% CI)						
Adjusted for GA and antenatal steroids	0.2 (−0.2 to 0.5)	.36	−0.0 (−0.5 to 0.5)	.89	0.3 (−0.1 to 0.8)	.13
Adjusted for GA, antenatal steroids, and sociodemographic variables[c]	-0.0 (-0.4–0.4)	.99	−0.1 (−0.6 to 0.5)	.77	0.1 (−0.4 to 0.6)	.74

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(continued)

SUPPLEMENTAL TABLE 6

Association between mode of conception and neurodevelopmental outcome measures at 5.5 years (multivariate complete case analysis) *(continued)*

Variable	MAR[a] vs Spontaneous conception		IO or IUI vs Spontaneous conception		IVF or IVF-ICSI vs Spontaneous conception	
	OR or MD (95% CI)[b]	*P* value	OR or MD (95% CI)[b]	*P* value	OR or MD (95% CI)[b]	*P* value
Total MABC-2 score<5th percentile[e]						
Adjusted for GA and antenatal steroids	0.66 (0.42–1.05)	.080	0.68 (0.36–1.27)	.23	0.65 (0.35–1.20)	.17
Adjusted for GA, antenatal steroids, and sociodemographic variables[c]	0.76 (0.44–1.31)	.32	0.78 (0.39–1.59)	.50	0.73 (0.36–1.49)	.39

CI, confidence interval; *GA*, gestational age; *ICSI*, intracytoplasmic sperm injection; *IQ*, intelligence quotient; *IUI*, intrauterine insemination; *IVF*, in vitro fertilization; *MABC-2*, Movement Assessment Battery for Children-Second Edition (Henderson, 2007); *MAR*, medically assisted reproduction; *MD*, mean difference; *OI*, ovulation induction; *OR*, odds ratio; *SD*, standard deviation.

[a] MAR corresponds to the whole range of MAR techniques (ie IO, IUI, IVF, and IVF-ICSI); [b] The reported measures of association are OR, except for Full Scale IQ and total MABC-2 score where MDs are reported. The generalized estimating equations approach is used to consider the correlation between twins or triplets; [c] Sociodemographic factors adjusted for were maternal age, parity, education level, employment status, living with a partner, smoking during pregnancy, country of birth, and parents' socioeconomic status; [d] Full Scale IQ, measured by the Wechsler Preschool and Primary Scale of Intelligence-Fourth edition[26]; [e] Cutoff of the distribution related to a reference group born at term[27]; [f] Severe or moderate cerebral palsy, severe or moderate sensory disabilities, or Full scale IQ <2 SDs below the mean of a reference population; [g] Among children without cerebral palsy, without severe or moderate sensory disabilities, and with Full Scale IQ ≥2 SDs below the mean of a reference population.

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