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Neurodevelopmental Outcomes After Assisted Reproductive Technologies

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Abstract

OBJECTIVE—To compare children's cognitive, motor, and language development at 2 years of age after assisted reproductive technologies (ARTs) relative to natural conception.

METHODS—The 3D-Study (2010–2012) is a prospective cohort study, which sought to improve the understanding among perinatal events, obstetric outcomes, and child development. A total of 2,366 pregnant women were recruited, of whom 278 conceived with ART: ovarian stimulation, intrauterine sperm insemination, in vitro fertilization, intracytoplasmic sperm injection, or in vitro maturation. Natural conception was defined as the unassisted establishment of pregnancy. Cognitive, motor, and language neurodevelopmental outcomes were compared between ART and natural conception groups at 24 months using the Bayley Scales of Infant and Toddler Development, 3rd edition, and the MacArthur-Bates Communicative Development Inventories. Adjusted linear regression models evaluated the effect of ART on neurodevelopmental outcomes using natural conception as a reference.

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RESULTS—A total of 175 children in the ART group (62.9%) and 1,345 children in the natural conception group (64.4%) underwent neurodevelopmental assessment at 24 months postpartum. After adjusting for relevant confounders, children born after ART showed no difference in Bayley scales' cognitive scores (B_1 [standard error]=−1.60 [0.9], 95% confidence interval [CI] −3.36 to 0.16), composite motor scores (B_1 [standard error]=−1.33 [1.0], 95% CI −3.29 to 0.63), or MacArthur-Bates language scores (B_1 [standard error]=−0.28 [2.1], 95% CI −4.39 to 3.83). No difference was observed when independent ART techniques were compared nor when comparing in vivo (ovarian stimulation or intrauterine insemination) or in vitro (in vitro fertilization, intracytoplasmic sperm injection, or in vitro maturation) techniques (P>.05).

CONCLUSION—Children born after ART had similar cognitive, motor, and language development as children born after natural conception at 2 years of age. These findings may be useful in the clinical counseling of patients undergoing ART.

Technologic advances and changing social paradigms have led to the increased use of assisted reproductive technologies (ARTs) for the purposes of procreation.[1] The main techniques to treat infertility include: ovarian stimulation and intrauterine sperm insemination as well as techniques whereby oocytes and sperm are handled in vitro, like in vitro fertilization (IVF), intracytoplasmic sperm injection, and in vitro maturation.[2–4] We refer to ART as any of the aforementioned infertility treatments leading to conception outside natural coitus.

In Canada, reports indicate that the use of fertility treatments increased by 50% over the past decade.[1,5] Although the short-term perinatal outcomes after ART are well established, long-term neurodevelopmental outcomes, including cognitive, motor, and language development, are still a source of controversy.[3,6–9]

A review from the National Institutes of Health recognized that "lingering data gaps [exist] in the equivocal literature for many neurodevelopmental disabilities relative to ART" and that "…cohorts with longitudinal assessment…of neurodevelopment…are paramount for the development of empirically-based guidance…."[10] Similarly, the largest systematic review of more than 80 studies addressing long-term neurodevelopment after ART concluded that additional data were required to determine the true effect of fertility treatments on these outcomes.[3]

In our study, we tested the hypothesis that neurodevelopment at 2 years is related to mode of conception. As such, using standardized and validated tools, the objective of this study was to compare children's cognitive, motor, and language development at 2 years of age after ART relative to natural conception.

MATERIALS AND METHODS

We analyzed data from the 3D-Study (Découvrir, Développer, Devenir), a prospective, longitudinal cohort carried out from 2010 to 2012 by the Integrated Research Network in Perinatology of Quebec and Eastern Ontario in Canada.[11,12] The 3D-Study recruited 2,366 women in their first trimester of pregnancy and their respective births across nine sites in the province of Quebec and gathered extensive data on the mother–father–child triad from

conception until 2 years postpartum. At 2 years postpartum, children underwent cognitive, motor, and language testing using the Bayley Scales of Infant and Toddler Development, 3rd edition, and the MacArthur-Bates Communicative Development Our primary objective was to compare the neurodevelopment in children born with the help of fertility treatments (exposed) relative to those born off pregnancies conceived naturally (controls). Our secondary objective was to describe baseline medical and sociodemographic differences between an ART and a non-ART cohort in Quebec.

The 3D-Study enrolled: 1) pregnant women between 8 0/7 and 13 6/7 completed weeks of gestation and 2) planning delivery in a 3D-Study–associated hospital. Exclusion criteria included: 1) women younger than 18 years of age, 2) illegal intravenous drug users, 3) non-English or French speakers, 4) severe illnesses or life-threatening conditions, and 5) multiple pregnancies, which includes twins or higher order multiples and mothers whose previous pregnancies had been enrolled in the study.

The Bayley Scales of Infant and Toddler Development, 3rd edition, is a validated and standardized developmental assessment for children aged 1–42 months that includes five independent scales (cognitive, motor [fine and gross], language, adaptive function, and socioemotional).[13] In our study, we used the cognitive scale, which assesses cognitive processes like memory, exploration, manipulation, and sensorimotor development as well as the motor scale, which is divided into the fine motor and gross motor subtests and evaluates quality of movement, sensory integration, perceptual–motor integration, prehension, and other milestones. Each scale consists of a series of developmental play tasks. Scale-specific raw scores of completed items are then converted to scaled scores and to composite scores as a function of age. For the fine and gross motor subtests, only scaled scores are available. The scaled and composite scores are then compared with normalized scores taken from typically developing children of similar age. Mean is set at 10 and 100 with a standard deviation of 3 and 15 for the scaled scores (fine and gross motor) and the composite score (cognitive, motor), respectively. The Bayley scales (3rd edition) have established test–retest reliability, internal consistency as well as convergent and divergent validity.[13] In our study, trained individuals who were blinded to the exposure administered the tool.

To evaluate language development, we used the toddler short form of MacArthur-Bates Communicative Development Inventories,[14] a norm-referenced parent questionnaire that captures important information about a child's developing abilities. Specifically, we used a 100-word vocabulary production checklist and a question about early word combinations, which can be reported on a 100-point scale.[14,15] The English MacArthur-Bates toddler short form has established reliability as well as content and concurrent validity.[14,15] A French version of the short form has been adapted for French-speaking children in Québec using the approach described by Fenson et al.[14]

Based on the proportion of children having undergone the assessments (ART, n=175; natural conception, n=1,345), a power calculation was conducted to determine whether a minimal clinically significant difference in the Bayley scales (3rd edition) scores could be detected. Using previously reported mean and variance composite cognitive scores at 24 months of

age, we used a two-sided type I error (α) of 5% and obtained 98.57% power to detect a 5-point difference between groups.[16]

We carried out our analysis in four steps. First, we described each subgroup according to their baseline demographic and gestational characteristics (Table 1). We included descriptors of infertility diagnoses for patients undergoing ART and those defined as sub-fertile (Table 2). Subsequently, we described obstetric outcomes in the ART compared with natural conception group (Table 3).

We then evaluated the Bayley scales (3rd edition) (cognitive and motor) and MacArthur-Bates (language) scores for each mode of conception using χ^2 and analysis of variance statistical testing to determine within-group variability. Finally, we applied linear regression models to evaluate both the crude and adjusted effects of ART on scale scores using the natural conception group as a reference. Estimates for individual ART techniques were calculated as were estimates for grouped modes of conception: in vivo (ovarian stimulation and intrauterine insemination) and in vitro (IVF, intracytoplasmic sperm injection, and in vitro maturation). Analyses were adjusted for parental age (years), family income (Canadian dollars), maternal ethnicity (Caucasian compared with not), maternal education (level), marital status (married compared with not), maternal history of depression (yes or no), maternal smoking intake, alcohol consumption during pregnancy (yes or no), antidepressant use (yes or no), and folic acid intake during pregnancy (yes or no). Sensitivity analyses were carried out to evaluate the robustness of the model adjusting for thyroid disease, breastfeeding status as well as removing single women and same-sex couples from our model. In accordance with a provincial policy of elective single embryo transfer during the study period, the vast majority of patients undergoing embryo transfer (IVF, intracytoplasmic sperm injection, in vitro maturation) in our study received a single embryo per cycle. An exemption was made if the patient was older than 35 years of age and had prior cycle failures, in which case the transfer of two embryos was considered. We sought and received approval from the institutional ethics review board at the CHU Sainte-Justine Center (acting as the central ethics review board) in Montreal, Quebec. All analyses were conducted using SAS 9.3.

RESULTS

Our final cohort consisted of 2,366 women carrying singleton pregnancies. We compared 278 pregnancies after ART with 2,088 pregnancies after natural conception. The ART cohort was comprised of the following techniques: stimulation (n=53), intrauterine insemination (n=79), IVF (n=32), intracytoplasmic sperm injection (n=105), and in vitro maturation (n=9). The spontaneous conception cohort was comprised of subfertile patients (n=490) and patients achieving natural conception at less than 6 months (n=1,598). Patients undergoing ART were more likely to be older, more educated, of lower parity, and with higher rates of thyroid disease. The later finding may be the result of more intense screening in the ART group as well as underlying thyroid dysfunction leading to infertility. On the other hand, mothers in the natural conception group were more likely to be Caucasian, multiparous, and with higher rates of caffeine, smoking, and alcohol consumption before and during pregnancy (Table 1).

In Table 2, infertility characteristics were compared between patients undergoing ART and those identified as being subfertile, who conceived after 6 months of trying. Patients having undergone ART had a longer time to conception and higher rates of underlying infertility diagnoses in both females and males ($P<.001$).

Table 3 presents obstetric and neonatal outcomes between both groups. Neonates born after ART were more likely to be of lower birth weight (3,279 g [interquartile range 697] compared with 3,356 g [interquartile range] 1,034), more likely to be born by cesarean delivery (36.5% compared with 25.1%), and to be admitted to the neonatal intensive care unit (7.7% compared with 3.9%). Although statistical differences were noted in the gestational age at birth, these are unlikely to be of clinical significance (38.4 weeks of gestation [interquartile range 2.0] compared with 38.8 weeks of gestation [interquartile range 2.0], $P=.006$).

A total of 175 of 278 children in the ART group (62.9%) and 1,345 of 2,088 in the natural conception group (64.4%) underwent neurodevelopmental assessments at 24 months. No significant differences were observed in cognitive (composite mean score-±standard deviation: 98.5±11.2 compared with 100.1±11.4, $P=.08$), fine motor (scaled mean score 11.4±2.3 compared with 11.6±2.7, $P=.41$), gross motor (scaled mean score 8.8±2.0 compared with 8.9±2.3, $P=.37$), or language scores (53.9±23.6 compared with 55.6±24.4, $P=.50$) (Table 4). Finally, Table 5 showcases the linear regression models. After adjusting for relevant confounders, children born after ART showed no difference in Bayley scales (3rd edition) cognitive composite scores (B_1 [standard error]=−1.60 [0.9], $\beta'=-0.045$, $P=.08$), composite motor scores (B_1 [standard error]=− 1.33 [1.0], $\beta'=-0.036$, $P=.18$), or MacArthur-Bates language scores (B_1 [standard error]=−0.28 [2.1], $\beta'=-0.003$, $P=.89$) relative to natural conception. No significant differences were observed when comparing in vivo and in vitro techniques separately ($P>.05$) nor when comparing independent techniques individually. However, our study was not powered to compare the latter (Appendix 2, available online at http://links.lww.com/AOG/A911). Sensitivity analyses showed no differences in the model estimates when adjusting for thyroid disease, breast-feeding rates nor when removing single women or same-sex couples from the model.

Relative to participants lost to follow-up in the ART cohort, mothers of children who underwent testing were more likely to be Caucasian and of higher income. Among the natural conception cohort, mothers of children who underwent testing were more likely to be Caucasian, older, of higher education and income, and of lower parity (Appendix 3, available online at http://links.lww.com/AOG/A911).

DISCUSSION

Creating families through ART raises a number of concerns about potentially adverse consequences for child development.[2,3,17–19] However, these concerns stem from largely retrospective studies with small sample sizes and heterogeneous methodologies.[20] By specifying the infertility treatments used, accounting for predictors of development, and using standardized testing, our prospective study overcomes some of these limitations and

provides reassuring results in that children born after ART appear to have similar cognitive, motor, and language skills than children born after natural conception at 2 years of age.

The recent Upstate KIDS Study sought to assess the same question in this report, notably, the association between the mode of conception and children's development.[9] According to its results, children's development at age 3 years appears independent on mode of conception.[9] Although the prospective nature of the KIDS study is a major strength, a number of its limitations are addressed by our study. Whereas the KIDS study recruited newborns, the 3D-Study recruited mothers during the first trimester, allowing us to prospectively gather data on prenatal factors that may have affected neurodevelopment such as antidepressant, folic acid, alcohol, and smoking exposure. Second, their study used the Age and Stage Questionnaires to assess neurodevelopment. Unlike the Bayley scales (3rd edition), which are administered by a third party blinded to the exposure, the Age and Stage Questionnaires require parental administration, which may introduce confirmatory bias.[21] Third, although the 3D-Study required a prospective, two-step verification of exposure including ovarian stimulation and intrauterine insemination, the KIDS study could not verify the validity of the exposure because there is no registry in the United States.[9] Nevertheless, the replication of similar findings in both studies despite the use of different methodologies is encouraging and may serve to reassure patients undergoing ART.

Each facet of neurodevelopment after ART has been studied previously. To date, two large systematic reviews of more than 80 studies addressed cognitive development after ART, concluding that, "there is sufficient data to support…no difference in development… between IVF and spontaneously conceived children"[3,20] and that "most studies showed no associations with cognitive…development."[3] Because we cannot preclude that differences in cognition may appear later in life, a follow-up of children from prospective studies such as this one may be necessary.

Similarly, prospective evidence of motor skills at 24 months of age evaluated with standardized testing is lacking in the literature. Although some studies do point to delays in motor development between 16 and 18 months,[22] our findings concur with the majority of the literature that motor development is not affected by the mode of conception.

Most of the controversy seems to be found in language development after ART.[7,22,23] As evidenced by the lack of consensus, there is a call for prospective evaluation of children's language skills after ART as we have done in our study, in which we find no significant difference in MacArthur-Bates scores at 24 months of age.

The strengths of the present study include: the use of a prospective cohort of pregnant women with up to 3 years of follow-up, the use of standardized tools administered by professionals blinded to exposure, and the analysis of a number of ART techniques. In addition, we adjusted for a vast array of pertinent confounders, including maternal depression, which is notably lacking in the literature.[24] Likewise, our study uses North American data, which may enhance external validity amongst Canadian and U.S. centers. Finally, we conducted sensitivity analyses, which confirmed the robustness of our model.

On the other hand, a number of limitations are worth mentioning. Although this study was powered to estimate the effect of ART as an overall category, it was not powered to detect a difference among individual techniques. Likewise, we considered the main ART technique as exposure and could not account for the type of cycle (natural compared with stimulated) used. Furthermore, although loss to follow-up rates were moderate in each group, a post hoc power calculation reveals adequate power to answer the study question. Moreover, given the study design, we were not able to untangle the effects of the underlying infertility from the ART technique used, because this is an example of confounding by indication. Finally, the children in our study population were young, and in certain cases, developmental characteristics may have a limited predictive value for long-term development.

All in all, the findings hereby presented may be useful in the clinical counseling of patients undergoing ART. Future prospective studies with long-term follow-up, powered to study individual ART techniques as well as evaluation of behavioral outcomes (such as attention deficit or hyperactivity and autism-like behaviors), are necessary.

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Table 1

Baseline Patient Characteristics According to Mode of Conception

Variable	ART (n=278)	No ART (n=2,088)	*P*
Maternal age (y)	34.9±4.5	31.6±4.5	<.001
Paternal age (y)	36.3±6.1	33.4±5.8	<.001
Maternal ethnicity			.015
Caucasian	202 (72.7)	1,681 (80.5)	
Black	23 (8.3)	135 (6.5)	
Latin American	17 (6.1)	101 (4.8)	
Asian	25 (9.0)	100 (4.8)	
Other	11 (4.0)	71 (3.4)	
Maternal education			
Postsecondary	267 (96.0)	1,927 (90.0)	.001
Household income (Canadian dollars)			.489
Less than 40,000	48 (17.2)	352 (16.9)	
40,000–80,000	80 (28.8)	634 (30.4)	
Greater than 80,000	131 (47.1)	1,003 (48.0)	
Refused to disclose	19 (6.8)	99 (4.7)	
Mother living alone	10 (3.6)	123 (5.9)	.812
Prepregnancy weight (kg) *	65.4±14.9	65.1±21.5	.630
Gravidity			<.001
1	132 (47.5)	728 (34.9)	
2	85 (30.6)	676 (32.4)	
Greater than 2	61 (21.9)	684 (32.8)	
Medical comorbidities			
Asthma	41 (14.8)	344 (16.5)	.464
Diabetes	3 (1.1)	18 (0.9)	.717
Thyroid disease	45 (16.2)	162 (7.8)	<.001
Major depression—past	20 (7.2)	156 (7.5)	.869
Major depression—present	2 (0.7)	19 (0.9)	.750
Hypertension	6 (2.2)	52 (2.5)	.736
Dyslipidemia	8 (2.9)	69 (3.3)	.706
Cardiovascular disease	6 (2.2)	19 (0.91)	.056
Seizures	10 (3.6)	27 (1.3)	.004
Anemia	47 (16.9)	343 (16.4)	.840
Sexually transmitted infection	27 (9.7)	235 (11.3)	.441
Folic acid intake	170 (61.2)	1,070 (51.3)	.002
Maternal caffeine intake			
During pregnancy	40 (14.4)	405 (19.4)	.045
Maternal smoking			
Before pregnancy	38 (13.7)	405 (19.4)	.022
During pregnancy	9 (3.2)	106 (5.1)	.180

Variable	ART (n=278)	No ART (n=2,088)	*P*
Maternal alcohol consumption			
Before pregnancy	157 (64.3)	1,418 (79.1)	<.001
During pregnancy	3 (1.1)	60 (2.9)	.081

ART, assisted reproductive technologies.

Data are mean±standard deviation or n (%) unless otherwise specified.

Gravidity is the total lifetime number of confirmed pregnancies including the current pregnancy.

* Values are rounded up.

Statistical tests used: χ^2, analysis of variance, *t* test.

Table 2

Infertility Characteristics Among Assisted Reproductive Technologies Compared With Subfertile Conceptions

Variable	ART (n=278)	Subfertile Conception (n=490)	*P*
Infertility for more than 6 mo	247 (88.9)	490 (100.0)	<.001
Infertility for more than 12 mo	225 (80.9)	253 (51.6)	<.001
Time to conception (mo)	29.1±28.0	11.3±13.3	<.001
Median	24.0	7.0	
Infertility diagnosis—female factors*			
Endometriosis	23 (8.2)	9 (1.8)	<.001
Tubal factor	28 (10.1)	3 (0.6)	<.001
PCOS+anovulation	85 (30.6)	30 (6.1)	<.001
Diminished ovarian reserve	28 (10.1)	7 (1.4)	<.001
Uterine malformation	1 (0.4)	2 (0.4)	<.001
Single woman	7 (3.3)	—	—
Same-sex couple	6 (2.8)	—	—
Unexplained infertility	39 (17.1)	2 (0.4)	<.001
Other female factor	23 (8.3)	10 (2.0)	<.001
Unknown	37 (13.3)	8 (1.63)	<.001
Infertility diagnosis—male factors*			
Oligozoospermia	42 (15.1)	4 (0.7)	<.001
Teratospermia	48 (18.0)	3 (0.5)	<.001
Azoospermia	18 (6.5)	0 (0.0)	—
Ejaculatory dysfunction	2 (0.7)	0 (0.0)	—

ART, assisted reproductive technologies; PCOS, polycystic ovary syndrome.

Data are n (%) or mean±standard deviation unless otherwise specified.

Subfertile conception is natural conception after 6 months or longer of having tried to conceive.

Statistical tests used: χ^2, analysis of variance, *t* test.

*Values are rounded up. Percentages may not add up to 100%, because multiple infertility diagnoses may exist in the same patient.

Table 3

Obstetric and Neonatal Outcomes According to Mode of Conception

Variable	ART (n=278)	No ART (n=2,088)	*P*
Fetal sex			
Male	129 (49.1)	987 (50.4)	.803
Gestational age (wk)	38.4±2.8	38.8±2.1	.006
IQR	2.0	2.0	
Birth weight (g)	3,279.0±638.9	3,356.9±525.8	.030
IQR	697	1,034	
Fetal presentation*			.233
Cephalic	243 (92.4)	1,823 (92.8)	
Breech	13 (4.9)	99 (5.0)	
Other	0 (0.0)	15 (0.7)	
Unknown	7 (2.7)	31 (1.5)	
Mode of delivery			.000
Vaginal	138 (52.5)	1,275 (64.9)	
Cesarean	96 (36.5)	494 (25.1)	
Vacuum	14 (5.3)	109 (5.5)	
Forceps	15 (5.7)	88 (4.5)	
NICU admission	20 (7.7)	75 (3.9)	.004
5-min Apgar score	9 (3–10)	9 (5–10)	.880
Congenital anomalies	10 (3.8)	60 (3.1)	.525

ART, assisted reproductive technologies; IQR, interquartile range; NICU, neonatal intensive care unit.

Data are n (%), mean±standard deviation, or median (range) unless otherwise specified.

Statistical tests used: χ^2, analysis of variance, *t* test.

*Values are rounded up.

Table 4

Analysis of Variance—Bayley Scales of Infant and Toddler Development, 3rd Edition, and MacArthur-Bates Communicative Development Inventories Scale Scores at 24 Months of Age

Variable	ART (n=175)	No ART (n=1,345)	*P*
Cognitive composite score	98.5±11.2	100.1±11.4	.079
Score range	65–130	55–145	
Motor composite score	100.8±9.8	101.8±12.2	.282
Score range	82–142	61–164	
Fine motor—scaled score	11.4±2.3	11.6±2.7	.414
Score range	7–18	3–19	
Gross motor—scaled score	8.8±2.0	8.9±2.3	.372
Score range	4–16	1–19	
MacArthur-Bates Scale score	53.9±23.6	55.6±24.4	.507
Score range	1–100	5–100	

ART, assisted reproductive technologies.

Data are mean±standard deviation or minimum–maximum unless otherwise specified.

MacArthur-Bates Scale Score: out of 100. In the present study, 8% of the sample responses were based on the English version of the inventory and the remaining children's responses were based on the French version. The mean scores and standard deviations were similar for both language groups.

Statistical test used: *t* test.

Table 5

Adjusted Linear Regressions of Neurodevelopmental Scores Among All Assisted Reproductive Technologies, In Vivo, and In Vitro Conceptions Relative to Natural Conception*

	All ART				In Vivo (OS+IUI)				In Vitro (IVF+ICSI+IVM)			
Variable	**B_1 (SE)**	**95% CI**	**β′**	***P***	**B_1 (SE)**	**95% CI**	**β′**	***P***	**B1 (SE)**	**95% CI**	**β′**	***P***
Cognitive composite score	−1.60 (0.9)	−3.36 to 0.16	−0.045	.080	−2.22 (1.2)	−4.57 to 0.13	−0.048	.065	−0.60 (1.3)	−3.14 to 1.94	−0.013	.640
Motor composite score	−1.33 (1.0)	−3.29 to 0.63	−0.036	.186	−1.64 (1.3)	−4.18 to 0.90	−0.033	.222	−1.04 (1.4)	−3.78 to 1.70	−0.020	.467
Fine motor—scaled score	−0.24 (0.2)	−0.68 to 0.15	−0.030	.264	−0.26 (0.3)	−0.84 to 0.32	−0.024	.371	−0.22 (0.3)	−0.80 to 0.36	−0.020	.476
Gross motor—scaled score	−0.19 (0.2)	−0.58 to 0.20	−0.026	.331	−0.26 (0.3)	−0.84 to 0.32	−0.028	.300	−0.12 (0.3)	−0.70 to 0.47	−0.013	.642
MacArthur-Bates Scale Score	−0.28 (2.1)	−4.39 to 3.83	−0.003	.894	2.18 (2.8)	−3.30 to 7.66	0.016	.448	−2.88 (2.8)	−8.36 to 2.60	−0.021	.320

ART, assisted reproductive technology; OS, ovarian stimulation; IUI, intrauterine insemination; IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection; IVM, in vitro maturation; B_1, linear regression β coefficient; SE, standard error; CI, confidence interval; β′, standardized linear regression β coefficient.

Whereas B_1 represents the change in the score units of each scale for ART conception relative to a natural conception, β′ represents that change as a factor of standard deviation units. Both are interchangeable.

Non-ART and natural conception as a reference.

Statistical test used: adjusted linear regression.

*Adjusted for maternal age, paternal age, maternal education, income, ethnicity, marital status, smoking intake, alcohol consumption during pregnancy, history of depression, antidepressant use, and folic acid intake.