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Infertility, infertility treatment and psychomotor development: Danish National Birth Cohort

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Summary

Babies born of infertile couples, regardless of treatment, have a higher risk of preterm birth and low birthweight, conditions associated with delayed development. We examined developmental milestones in singletons as a function of parental infertility [time to pregnancy (TTP) >12 months] and infertility treatment. From the Danish National Birth Cohort (1997–2003), we identified 37,897 singletons born of fertile couples (TTP ≤12 months), 4351 born of infertile couples conceiving naturally (TTP >12 months), and 3309 born after infertility treatment. When the children were about 18 months old, mothers reported 12 developmental milestones by responding to structured questions. We defined a failure to achieve the assessed milestone or the minimal numbers of milestones in a summary (motor, or cognitive/language skills) as delay. Naturally conceived children born of infertile couples had a pattern of psychomotor development similar to that of children born of fertile couples, but increasing TTP correlated with a modest delay. When the analysis was restricted to infertile couples (treated and untreated), children born after treatment showed a slight delay in cognitive/language development (odds ratio 1.24, [95% confidence interval 1.01, 1.53] for not meeting at least three out of six cognitive/language milestones); children born after intracytoplasmic sperm injection (ICSI) had the highest estimated relative risk of delay for most milestones, especially motor milestones. These results suggest that a long TTP may be associated with a modest developmental delay. Infertility treatment, especially ICSI, may be associated with a slight delay for some of these early milestones.

Keywords

child development; infertility; assisted reproductive techniques

Introduction

Infertility, usually defined as a failure to achieve a clinically recognized pregnancy after more than 12 months of unprotected intercourse [time to pregnancy (TTP) >12 months], affects about 10–20% of couples trying to become pregnant in many industrialized countries,¹ and an increasing number of couples seek medical treatment.²

Singletons born after assisted reproductive technology (ART) have a higher rate of adverse pregnancy outcomes, such as preterm delivery and reduced fetal growth,^{3–6} but a growing body of evidence suggests that infertility *per se*, or some of its determinants, may be related to these outcomes.^{6–11} Since both preterm delivery and reduced fetal growth are associated with delayed neurodevelopment,^{12, 13} the potential contribution of infertility and ART to children's development needs to be assessed. With respect to ART, few studies with acceptable size and quality have been performed on child health and development [see reviews^{14–16}]. Although most studies found no major psychomotor developmental delay in children born after in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI), methodological limitations of the published studies (e.g., a small sample size, or a high rate of dropouts) make it difficult to conclusively rule out adverse effects of ART on the development of children.

Using data from the Danish National Birth Cohort (DNBC),¹⁷ we examined developmental milestones as a function of time to pregnancy and infertility treatment in singletons born of planned pregnancies.

Methods

Study population

The DNBC was established to explore the importance of social, environmental, and lifestyle factors during pregnancy and early childhood on health and development of children.¹⁷ Women, recruited early in pregnancy, participated in four computer-assisted telephone interviews (two scheduled at 12 and 30 weeks of gestation and two scheduled when the child was 6 and 18 months' old, respectively).

Of 92,892 pregnancies recruited for the first interview (1997–2003), we excluded 2,700 that had ended before the first interview took place and 22,336 unplanned or partly planned pregnancies (with no or less reliable TTP), leaving 67,856 with a known TTP. We, additionally, excluded pregnancies with unknown infertility treatment status (N=29) and any pregnancies beyond the earliest from women who contributed more than one pregnancy to the study (N=3,973). We further excluded 299 pregnancies conceived with a treatment other than ICSI, IVF, intrauterine insemination (IUI), or hormonal treatment (HT). After identifying pregnancy outcomes by linking the cohort to the National Hospital Register and the Medical Birth Register, by means of the unique civil registration number, we excluded pregnancies ending in spontaneous or induced abortion, ectopic pregnancy, hydatidiform mola, and stillbirth (N=941), pregnancies with unknown outcome (N=44), and pregnancies resulting in multiple births (N=1,614), thus leaving 60,956 eligible singletons. Of these, we further excluded 15,373 babies whose mother did not participate in the 18-month interview, five for whom mother failed to provide information on developmental milestones, and 21 babies who were older than 25 months at the time of interview or with a missing interview date. The remaining 45,557 children (75% of the eligible) were then categorized as: A) 37,897 born of fertile couples (TTP ≤12 months), B) 4,351 born of infertile couples conceiving naturally (TTP >12 months), and C) 3,309 born after infertility treatment. Babies in group A were considered as born of fertile couples, whereas babies in groups B and C were categorized as born of infertile couples.

Participation in the 18-month interview

The overall participation rate in the 18-month interview was 74.8% for mothers of live-born singletons. Mothers who had received infertility treatment participated in the interview significantly more frequently than mothers in group A (77.1% vs. 74.5%), but comparable with mothers in group B (77.1% vs. 75.5%). Non-participants, compared with participants, were slightly younger (mean $\pm$ standard deviation: 29.4 $\pm$ 4.2 years vs. 29.8 $\pm$ 4.0 years) and of slightly lower social class (42.5% vs. 45.1% worked as managers, professionals or technicians), and their children were more frequently born preterm (5.5% vs. 4.2%). Participation among mothers of children born preterm was, however, independent of infertility status and treatment.

Pregnancy planning status, time to pregnancy, and infertility treatment

In the first interview, participants were asked if their pregnancy was planned, partly planned, or not planned. If the pregnancy was planned or partly planned, women were further asked for how long they had tried to become pregnant. The TTP response categories included “right away”, 1–2, 3–5, 6–12, and >12 months. If they reported a TTP of 6 months or more, women were also asked if they or their partner had received any infertility treatment. If a woman reported that she or her male partner had received infertility treatment, she could choose from a list including ICSI, IVF, IUI, and HT, or she could describe the treatment in her own words. If more than one procedure was reported, we classified the treatment according to the above sequence.

Developmental milestones

In the 18-month interview, the mother was asked 12 questions on developmental milestones of her child, including five concerning gross and fine motor performances, one concerning attention, and six concerning cognitive and language skills (available at <http://www.bsmb.dk/>). These questions were developed by an experienced child neuropsychologist with indepth knowledge of developmental scales and milestones for this age group. The questions were considered as the best option at that time given the conditions of the study (time and the telephone interviews).

While nine questions had a YES/NO answer, three required more detailed responses (sitting, walking, and naming things). For the age at which the child was able to sit or walk alone, we defined babies as delayed if they exceeded the 90th–95th centile of the distribution of age (in month) for achieving the milestone, ie, 9 months for sitting alone (95%) and 16 months for walking alone (93%). For talking, the mother could choose between five categories to describe how many things her child could mention by name: 0–10, 11–25, 26–100, 101–300, and 300 + words, with one additional category of free text.

We used a cut-off of 10 words to obtain the highest proportion of children achieving this ability (42%). There were two other milestones (one concerning cognition, one concerning language) that only about half of children had reached at the time of interview. These three milestones would have very limited values in the assessment. We defined a failure to achieve the assessed milestone as a developmental “delay”.

An estimate of 5–10% of the pediatric population has a developmental disability.¹⁸ To summarize motor and cognitive/language milestones, we also defined as “normal” developed those children who had reached four of the five motor and three of the six cognitive/language milestones, respectively, corresponding 95% of the children for each summary. As a result, we considered children who did not achieve the minimum number of milestones as developmentally “delayed”.

Statistical analysis

We calculated odds ratio (OR) and 95% confidence interval (CI) for delay of each developmental milestone or summary by using logistic regression in STATA 9.1 (StataCorp, College Station, Texas, USA). We first compared children born of infertile couples, untreated and treated, with children born of fertile couples. We then restricted the analyses to infertile couples to assess the potential effect of treatment. Finally, we estimated the effect of TTP in all children without treatment, and we performed a test for trend for the effect of TTP by including in the model the categories of TTP as a continuous variable. We additionally used Cox regression to analyse age at sitting or walking alone as continuous outcomes.

We adjusted in the models for child's age (in months) at the time of the interview assessing milestones and potential confounders, such as maternal age at conception (<25, 25–29, 30–34, 35+ years) and parental occupational status (as defined in table 1, footnote). Parity is an intermediate variable between infertility and outcome, but a potential confounder for infertility treatment. We thus checked whether parity impacted the effect estimates of infertility and infertility treatment by including and excluding parity in the models. We also examined whether gestational age at birth mediated the effect estimates by including gestational age in the regression models.

The study was approved by the Danish Data Protection Agency (reference no. 2005-41-5488), and the Danish National Birth Cohort Steering Committee granted authorization for use of data from the DNBC (reference no. 2005-10).

Results

Characteristics of parents and children in the three groups are shown in Table 1. Among infertile couples, with or without treatment, mothers were older and more often primiparous. The mean age of the children at the time of the interview scheduled at 18 months was 19.5 months (range of 17–25 months), and was similar across the groups of studied children.

Compared with children born of fertile couples, children born of infertile couples conceiving naturally had a similar pattern of motor, attention, and cognitive/language development, whereas children born after treatment appeared to have a slight delay in motor and cognitive/language development (Table 2). When treated infertile couples were compared with untreated infertile couples (last three columns of Table 2), most of the effect estimates associated with treatment were reduced, but no more than 10%.

Even though the majority of children born after different treatment procedures had a similar pattern of milestones achievement to that of children born of untreated infertile couples, children conceived after ICSI had the highest effect estimates for a delay in most of the milestones (Table 3).

Longer TTP appeared to be associated with a delay in achieving the assessed milestones, in particular cognitive/language development (Table 4).

With regard to sitting or walking alone, we obtained similar results when using Cox regression models (data not shown).

We further tried to identify a subgroup of children who had not achieved any of the assessed milestones as with severe developmental delay (N=25). We found that untreated infertile couples had a similar adjusted risk as fertile couples (OR=0.84, 95% CI 0.19–3.66), while treated infertile couples had more than doubled adjusted risk compared with fertile couples (OR=2.26, 95% CI 0.72–7.08).

Several covariates were included in our analyses. Increasing maternal age was consistently associated with a delay in the examined developmental milestones. Higher parity was associated with earlier development in motor performance, attention, and cognition, but with a delay in language skills. Lower social class, younger age of child at interview, and shorter gestational age at birth were associated with delayed development. However, parity had little impact on the effect estimates of infertility and a modest impact on the effect estimates of infertility treatment (around 10 % changes in estimates). Gestational age had little impact on all the effect estimates, and restricting analyses to term births did not change the estimates either (data not shown). Overall, maternal age and parity were the most important factors that impacted the effect estimates of infertility or infertility treatment in our analyses.

Discussion

Overall, children of infertile couples reached developmental milestones similar to what we saw for children of fertile couples around 18 months of age. However, time to pregnancy in untreated couples correlated with psychomotor development, particularly cognitive/language development. Slightly more children born after infertility treatment, especially ICSI, showed a delay in the assessed milestones.

All children, regardless of outcome, were followed up in the same way from pregnancy to the time of the 18-month interview, provided that the mothers had not been lost to follow-up. Previous studies usually enrolled control children from nurseries or schools, and these volunteers may not have been drawn from the same population as the cases. Agreement to participate in the cohort was given before the child was born and was thus blinded to the outcome, as was the assessment of TTP. We had a fairly high participation rates for the interview assessing developmental milestones across all groups of mothers, and non-responses were mainly due to unsuccessful attempt to reach the participants by phone. Participation could also have been dependent on how well the child was doing, but this would cause bias only if refusal to respond also depended on infertility (or treatment) status. This could be the case, but we found no differential participation among mothers of children born preterm.

We included only planned pregnancies in order to control for unmeasured “parental attention to child”, which could differ depending on how much the pregnancy was desired. Unplanned (and partly planned) pregnancies are likely to be from more fertile couples than the ones examined here. However, children born of unplanned and partly planned pregnancies had a pattern of developmental milestones largely similar to those of couples with a TTP ≤ 12 months (data not shown).

We had the opportunity to adjust for several covariates in the analyses. The effects of these factors on developmental milestones we saw are in line with the literature.^{19–21} On the other hand, we did not control for other potential environmental or genetic factors.

Mothers provided their own assessment of their child’s developmental milestones, and they are probably the ones that know their child best. This assessment has, however, a subjective basis, even though mothers responded to structured questions administered by trained female interviewers. There appears to be good agreement on assessment of psychomotor development in children between parents’ and pediatricians’ reports.^{22,23} Most of the children were able to sit without support before 9 months of age and to walk without support before 16 months of age, consistent with the literature.²⁴ As expected, children born preterm had a delay in motor and cognitive/language development. However, children born of infertile couples, particularly after treatment, are so desired that these couples may have assessed their child’s milestones achievement differently (likely overestimated) from fertile parents, which would shift the effect estimates on “delay” towards low values.

The children in our study population were young, and a slight delay at a young age may have a limited predictive value for long term development, although children who develop faster during their first year of life have been shown to attain higher levels of education in adolescence and adulthood.²⁵

Most previous studies reported no major psychomotor developmental delay in ART children.^{15,26–30} Bowen et al reported an increased risk of mild developmental delay at 1 year among children born after ICSI,³¹ but this finding was dismissed in a 5-year follow-up study.³² The most recent study from the Netherlands found that motor outcomes of 5–8 years old singletons born at term after ICSI or IVF were similar, while children born after ICSI deviated slightly from naturally conceived controls.³³ These and our findings are, in general, reassuring, but also suggest that children born after infertility treatment, in particular ICSI, may have some delay in psychomotor development. The slight delay may be due to the determinants of a more severe form of infertility. However, the possible effects of ovarian stimulation and in-vitro procedures cannot be ruled out, and ICSI could interfere with sperm selection that likely occurs during natural fertilization.

The majority of children born of infertile couples in this cohort, regardless of whether they were conceived with or without infertility treatment, had a pattern of psychomotor development similar to that of children born of fertile couples. A longer waiting time to pregnancy was, however, associated with a slight delay in psychomotor development in couples who received no infertility treatment. Infertility treatment, especially ICSI, may be associated with a slight delay for some of the early milestones. However, whether this has any long-term consequences is unknown, and to evaluate this we need long-term follow-up of children born of subfecund parents.

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Table 1
The characteristics of the study population according to time to pregnancy and infertility treatment

	Group A: Singletons born of fertile couples (TTP ≤12 months)		Group B: Singletons born of infertile couples conceiving naturally (TTP >12 months)		Group C: Singletons born after infertility treatment	
	n	%	n	%	n	%
Total	37897	100.0	4351	100.0	3309	100.0
Maternal age, years						
<25	4362	11.5	330	7.6	112	3.4
25–29	17310	45.7	1636	37.6	1034	31.2
30–34	12832	33.9	1670	38.4	1400	42.3
35+	3393	9.0	715	16.4	763	23.1
Parity						
0	17844	47.1	2315	53.2	2433	73.5
1+	20038	52.9	2032	46.7	873	26.4
Missing	15	0.0	4	0.1	3	0.1
Maternal occupation^a						
High	17166	45.3	1743	40.1	1625	49.1
Medium	12963	34.2	1771	40.7	1157	35.0
Low	1510	4.0	279	6.4	119	3.6
Students	3357	8.9	224	5.1	148	4.5
Unemployed	2901	7.7	334	7.7	260	7.9
Paternal occupation^a						
High	17304	45.7	1786	41.0	1645	49.7
Medium	13089	34.5	1635	37.6	1017	30.7
Low	3776	10.0	574	13.2	355	10.7
Unemployed	2537	6.7	217	5.0	184	5.6
Unknown	1191	3.1	139	3.2	108	3.3
Preterm birth (<37 weeks)						
No	36469	96.2	4105	94.3	3091	93.4
Yes	1428	3.8	246	5.7	218	6.6

^a Occupational status: high (managers, professionals and technicians), medium (clerks, service and sales workers, skilled agricultural workers, and craft workers), low (unskilled workers), students, and unemployed or unknown.

Table 2

Percentages and odds ratios (ORs) with 95% confidence intervals (CIs) of “delay” (not meeting) of the assessed developmental milestones for singletons born of fertile couples (Group A), born of infertile couples conceiving naturally (Group B), and born after infertility treatment (Group C). Comparisons: Group B vs. Group A, Group C vs. Group A, and Group C vs. Group B.

	Group A		Group B				Group C					
	“Delay” % Developmental milestones	“Delay” % Gross motor	Group B vs. Group A		“Delay” % Fine motor	Group C vs. Group A		Group C vs. Group B		Adjusted OR ^b [95% CI]		
			Crude OR	Adjusted OR ^a [95% CI]		Crude OR	Adjusted OR ^a [95% CI]	Crude OR	Adjusted OR ^a [95% CI]			
Sitting without support at 9 months of age	5.2	5.8	1.13	1.06 [0.92, 1.23]	1.06 [0.92, 1.22]	6.4	1.25	1.19 [1.02, 1.38]	1.20 [1.02, 1.40]	1.11	1.10 [0.90, 1.34]	1.08 [0.88, 1.33]
Walking without support at 16 months of age	7.3	8.1	1.12	1.08 [0.96, 1.21]	1.07 [0.95, 1.20]	8.8	1.22	1.16 [1.02, 1.32]	1.12 [0.98, 1.28]	1.09	1.07 [0.91, 1.26]	1.05 [0.89, 1.25]
Going upstairs with support	4.2	4.6	1.09	1.04 [0.90, 1.22]	1.03 [0.88, 1.20]	4.7	1.11	1.08 [0.91, 1.28]	1.03 [0.86, 1.23]	1.02	1.04 [0.83, 1.29]	1.08 [0.86, 1.35]
Taking off socks and shoes when asked to	17.9	18.7	1.05	1.08 [0.99, 1.17]	1.02 [0.94, 1.11]	20.0	1.14	1.17 [1.07, 1.29]	1.01 [0.92, 1.11]	1.09	1.09 [0.97, 1.22]	0.98 [0.87, 1.11]
Drinking from an ordinary cup without help	1.2	1.5	1.26	1.15 [0.88, 1.49]	1.16 [0.89, 1.51]	1.5	1.28	1.21 [0.90, 1.63]	1.25 [0.92, 1.70]	1.01	1.07 [0.73, 1.57]	1.12 [0.76, 1.66]
Motor summary:												
Meeting at least 4 milestones	5.5	6.1	1.12	1.06 [0.92, 1.22]	1.04 [0.91, 1.20]	7.0	1.29	1.23 [1.06, 1.42]	1.16 [1.00, 1.35]	1.15	1.17 [0.96, 1.42]	1.18 [0.96, 1.44]
Attention	18.7	18.7	1.01	1.01 [0.93, 1.10]	0.97 [0.89, 1.05]	21.0	1.16	1.17 [1.07, 1.28]	1.04 [0.95, 1.14]	1.15	1.13 [1.01, 1.27]	1.07 [0.95, 1.21]
Cognition	3.0	3.3	1.09	1.03 [0.87, 1.24]	1.03 [0.86, 1.23]	3.9	1.32	1.26 [1.05, 1.53]	1.23 [1.02, 1.49]	1.21	1.23 [0.96, 1.58]	1.21 [0.94, 1.56]
Making marks on table or paper	5.1	6.5	1.28	1.22 [1.07, 1.39]	1.16 [1.01, 1.32]	6.8	1.36	1.38 [1.20, 1.60]	1.18 [1.02, 1.37]	1.07	1.14 [0.95, 1.37]	1.06 [0.88, 1.29]
Turning the picture right when looking in a book	49.3	49.5	1.01	0.96 [0.90, 1.03]	1.03 [0.96, 1.10]	48.5	0.97	0.94 [0.87, 1.01]	1.12 [1.04, 1.21]	0.96	0.98 [0.90, 1.08]	1.07 [0.97, 1.18]
Language	2.6	3.1	1.20	1.11 [0.92, 1.33]	1.16 [0.97, 1.40]	3.0	1.14	1.07 [0.87, 1.33]	1.24 [0.99, 1.54]	0.95	0.98 [0.75, 1.28]	1.05 [0.79, 1.39]
Using word-like sounds to tell what he/she wants	57.8	59.1	1.06	0.98 [0.92, 1.05]	1.03 [0.97, 1.11]	56.5	0.95	0.88 [0.81, 0.94]	1.02 [0.94, 1.10]	0.90	0.90 [0.82, 0.98]	0.99 [0.89, 1.09]
Using two-word sentences	58.0	58.2	1.01	0.96 [0.90, 1.02]	0.99 [0.93, 1.06]	57.8	0.99	0.94 [0.87, 1.01]	1.04 [0.96, 1.12]	0.98	0.99 [0.90, 1.08]	1.04 [0.95, 1.15]
Cognitive/language summary:	4.6	5.5	1.21	1.11 [0.96, 1.29]	1.14 [0.98, 1.31]	6.2	1.37	1.31 [1.12, 1.53]	1.39 [1.19, 1.64]	1.14	1.20 [0.98, 1.47]	1.24 [1.01, 1.53]
Meeting at least 3 milestones												

Logistic regression.

^a Adjusted for maternal age, parental occupational status, and child's age at interview (months).

^b Adjusted for maternal age, parity, parental occupational status, and child's age at interview (months). Additional adjustment for gestational age at birth did not change the effect estimates.

Table 3
Percentages and odds ratios (ORs) with 95% confidence intervals (CIs) of “delay” (not meeting) of the assessed developmental milestones for singletons born after different types of infertility treatment. Reference: singletons born of infertile couples who conceived naturally (Group B)

Developmental milestones	Intracytoplasmic sperm injection (N=309)			In vitro fertilization (N=1153)			Intrauterine insemination (N=1029)			Hormonal treatment (N=818)		
	“Delay” %	Crude OR	Adjusted OR ^a [95% CI]	“Delay” %	Crude OR	Adjusted OR ^a [95% CI]	“Delay” %	Crude OR	Adjusted OR ^a [95% CI]	“Delay” %	Crude OR	Adjusted OR ^a [95% CI]
Gross motor												
Sitting without support at 9 months of age	7.8	1.39	1.33 [0.84, 2.09]	5.9	1.02	0.94 [0.70, 1.27]	6.5	1.14	1.13 [0.84, 1.51]	6.3	1.10	1.14 [0.83, 1.57]
Walking without support at 16 months of age	11.7	1.50	1.40 [0.96, 2.04]	9.4	1.18	1.10 [0.86, 1.40]	7.3	0.90	0.87 [0.67, 1.14]	8.7	1.08	1.10 [0.84, 1.44]
Going upstairs with support	4.9	1.08	1.11 [0.63, 1.95]	4.2	0.91	0.96 [0.69, 1.35]	4.2	0.92	0.98 [0.70, 1.38]	5.8	1.28	1.32 [0.95, 1.83]
Fine motor												
Taking off socks and shoes when asked to	22.1	1.23	1.06 [0.79, 1.41]	21.2	1.16	1.04 [0.88, 1.24]	19.0	1.02	0.94 [0.78, 1.12]	18.9	1.01	0.94 [0.77, 1.14]
Drinking from an ordinary cup without help	1.9	1.31	1.58 [0.66, 3.76]	1.4	0.93	1.01 [0.56, 1.81]	1.5	0.97	1.09 [0.61, 1.94]	1.6	1.06	1.16 [0.63, 2.13]
<i>Motor summary:</i>												
<i>Meeting at least 4 milestones</i>	93	1.58	1.60 [1.04, 2.48]	7.2	1.19	1.21 [0.91, 1.60]	6.2	1.02	1.06 [0.79, 1.43]	6.8	1.12	1.15 [0.84, 1.57]
Attention												
Being occupied alone with the same thing for at least 15 minutes	24.4	1.40	1.22 [0.92, 1.61]	21.2	1.16	1.05 [0.88, 1.24]	19.3	1.04	0.96 [0.81, 1.15]	21.7	1.20	1.18 [0.98, 1.42]
Cognition												
Bringing things when told to	4.6	1.42	1.45 [0.81, 2.58]	4.0	1.23	1.21 [0.84, 1.73]	3.8	1.17	1.19 [0.82, 1.72]	3.8	1.17	1.17 [0.78, 1.74]
Making marks on table or paper	6.6	1.02	1.01 [0.63, 1.63]	7.1	1.11	1.09 [0.83, 1.43]	6.4	0.99	0.99 [0.75, 1.32]	7.2	1.12	1.12 [0.83, 1.51]
Turning the picture right when looking in a book	47.0	0.90	1.07 [0.84, 1.36]	48.2	0.95	1.09 [0.95, 1.26]	47.3	0.92	1.01 [0.87, 1.16]	51.2	1.07	1.13 [0.97, 1.32]
Language												
Using word-like sounds to tell what he/she wants	3.9	1.26	1.49 [0.80, 2.77]	2.7	0.86	0.92 [0.61, 1.40]	2.4	0.78	0.87 [0.56, 1.35]	3.7	1.19	1.28 [0.85, 1.92]
Mentioning more than 10 names of different things	51.8	0.74	0.86 [0.68, 1.09]	55.7	0.87	0.94 [0.82, 1.08]	57.5	0.94	1.01 [0.87, 1.16]	58.1	0.96	1.06 [0.91, 1.24]
Using two-word sentences	57.0	0.95	1.04 [0.81, 1.32]	55.6	0.90	0.94 [0.82, 1.09]	58.4	1.01	1.05 [0.91, 1.21]	60.5	1.10	1.16 [1.00, 1.36]

Developmental milestones	Intracytoplasmic sperm injection (N=309)			In vitro fertilization (N=1153)			Intrauterine insemination (N=1029)			Hormonal treatment (N=818)		
	“Delay” %	Crude OR	Adjusted OR ^a [95% CI]	“Delay” %	Crude OR	Adjusted OR ^a [95% CI]	“Delay” %	Crude OR	Adjusted OR ^a [95% CI]	“Delay” %	Crude OR	Adjusted OR ^a [95% CI]
<i>Cognitive/language summary:</i>												
<i>Meeting at least 3 milestones</i>	5.9	1.08	1.24 [0.74, 2.09]	6.2	1.13	1.25 [0.93, 1.69]	5.6	1.02	1.12 [0.82, 1.53]	7.1	1.31	1.37 [1.00, 1.86]

Logistic regression.

^a Adjusted for maternal age, parity, parental occupational status, and child’s age at interview (months).

Table 4
Odds ratios (ORs) with 95% confidence intervals (CIs) of “delay” (not meeting) of motor, attention, and cognitive/language skills in singletons born of untreated couples according to time to pregnancy

Time to pregnancy, months	“Delay” n (%)	Crude OR	Adjusted OR ^a [95% CI]	Adjusted OR ^b [95% CI]
Motor performances^c				
0–2	1,016 (5.3)	1.00	1.00 reference	1.00 reference
3–5	503 (5.6)	1.06	1.06 [0.95, 1.18]	1.05 [0.94, 1.17]
6–12	398 (5.9)	1.12	1.10 [0.98, 1.24]	1.09 [0.96, 1.23]
>12	243 (6.1)	1.16	1.10 [0.95, 1.27]	1.07 [0.93, 1.24]
<i>p</i> for trend			0.078	0.16
Attention^d				
0–2	3,731 (18.1)	1.00	1.00 reference	1.00 reference
3–5	1,872 (19.4)	1.09	1.09 [1.02, 1.15]	1.06 [1.00, 1.13]
6–12	1,404 (19.3)	1.09	1.08 [1.01, 1.16]	1.05 [0.98, 1.12]
>12	808 (18.7)	1.04	1.05 [0.97, 1.15]	1.00 [0.92, 1.09]
<i>p</i> for trend			0.026	0.43
Cognitive/language skills^e				
0–2	845 (4.4)	1.00	1.00 reference	1.00 reference
3–5	420 (4.6)	1.06	1.05 [0.93, 1.18]	1.06 [0.94, 1.19]
6–12	358 (5.2)	1.21	1.16 [1.02, 1.32]	1.18 [1.04, 1.34]
>12	223 (5.5)	1.28	1.16 [0.99, 1.35]	1.19 [1.02, 1.39]
<i>p</i> for trend			0.010	0.004

Logistic regression.

^a Adjusted for maternal age, parental occupational status, and child’s age at interview (months).

^b Adjusted for maternal age, parity, parental occupational status, and child’s age at interview (months).

^c Motor performances: at least 4 out of 5 milestones.

^d Attention: 1 milestone.

^e Cognitive/language skills: at least 3 out of 6 milestones.