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

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Summary

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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 reproduction*, *time to pregnancy*.

Introduction

Infertility, usually defined as a failure to achieve a clinically recognised 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 industrialised 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* fertilisation (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 TTP 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 2700 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. Additionally, we 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 ($n = 3973$). 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 mole, and stillbirth ($n = 941$), pregnancies with unknown outcome ($n = 44$), and pregnancies resulting in multiple births ($n = 1614$), 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 the 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 categorised as: (A) 37 897 born of fertile couples (TTP $\leq$ 12 months), (B) 4351 born of infertile couples conceiving naturally (TTP > 12 months), and (C) 3309 born after infertility treatment. Babies in group A were considered as born of fertile couples, whereas babies in groups B and C were categorised 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 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.ssi.dk/graphics/html/bsmb/UKInt4.pdf). These questions were developed by an experienced child neuropsychologist with in-depth 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 percentile of the distribution of age (in months) for achieving the milestone, i.e. 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 paediatric population had a developmental disability.[18] To summarise motor and cognitive/language milestones, we defined as 'normal' those children who had reached four of the five motor and three of the six cognitive/language milestones, corresponding to 95% of the children for each summary measure. As a result, we considered the 5% of children who did not achieve the minimum number of milestones as developmentally 'delayed'.

Statistical analysis

We calculated the odds ratio (OR) and 95% confidence interval [CI] for delay of each developmental milestone or summary measure by using logistic regression in STATA 9.1 (StataCorp, College Station, TX, 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 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 influenced 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 DNBC Steering Committee granted authorisation 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 17–25 months), and was similar across the groups of children studied.

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 by 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

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

	Group A	Group B	Group C
	n (%)	*n* (%)	*n* (%)
Total	37 897 (100.0)	4351 (100.0)	3309 (100.0)
Maternal age (years)			
<25	4 362 (11.5)	330 (7.6)	112 (3.4)
25–29	17 310 (45.7)	1636 (37.6)	1034 (31.2)
30–34	12 832 (33.9)	1670 (38.4)	1400 (42.3)
35+	3 393 (9.0)	715 (16.4)	763 (23.1)
Parity			
0	17 844 (47.1)	2315 (53.2)	2433 (73.5)
1+	20 038 (52.9)	2032 (46.7)	873 (26.4)
Missing	15 (0.0)	4 (0.1)	3 (0.1)
Maternal occupation[a]			
High	17 166 (45.3)	1743 (40.1)	1625 (49.1)
Medium	12 963 (34.2)	1771 (40.7)	1157 (35.0)
Low	1 510 (4.0)	279 (6.4)	119 (3.6)
Students	3 357 (8.9)	224 (5.1)	148 (4.5)
Unemployed	2 901 (7.7)	334 (7.7)	260 (7.9)
Paternal occupation[a]			
High	17 304 (45.7)	1786 (41.0)	1645 (49.7)
Medium	13 089 (34.5)	1635 (37.6)	1017 (30.7)
Low	3 776 (10.0)	574 (13.2)	355 (10.7)
Unemployed	2 537 (6.7)	217 (5.0)	184 (5.6)
Unknown	1 191 (3.1)	139 (3.2)	108 (3.3)
Preterm birth (<37 weeks)			
No	36 469 (96.2)	4105 (94.3)	3091 (93.4)
Yes	1 428 (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.
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.

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, defined as 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 double the 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 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 influenced the effect estimates of infertility or infertility treatment in our analyses.

Table 2. Percentages and odds ratios (OR) with 95% confidence intervals [CI] of 'delay' in (not meeting) 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)

	Group A	Group B				Group C						
			Group B vs. Group A				Group C vs. Group A			Group C vs. Group B		
Developmental milestones	Delay %	Delay %	Crude OR	Adjusted OR[a] [95% CI]	Adjusted OR[b] [95% CI]	Delay %	Crude OR	Adjusted OR[a] [95% CI]	Adjusted OR[b] [95% CI]	Crude OR	Adjusted OR[a] [95% CI]	Adjusted OR[b] [95% CI]
Gross motor												
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]
Fine motor												
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												
Being occupied alone with the same thing for at least 15 min	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												
Bringing things when told to	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												
Using word-like sounds to tell what he/she wants	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]
Mentioning more than 10 names of different things	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:												
Meeting at least 3 milestones	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]

Comparisons: Group B vs. Group A, Group C vs. Group A and Group C vs. Group B.
[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 (OR) with 95% confidence intervals [CI] of 'delay' in (not meeting) the assessed developmental milestones for singletons born after different types of infertility treatment

	Intracytoplasmic sperm injection ($n = 309$)			*In vitro* fertilization ($n = 1153$)			Intrauterine insemination ($n = 1029$)			Hormonal treatment ($n = 818$)		
Developmental milestones	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]
Motor summary:												
Meeting at least 4 milestones	9.3	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 min	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]
Cognitive/language summary:												
Meeting at least 3 milestones	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]

Reference: singletons born of infertile couples who conceived naturally (Group B).

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

Table 4. Odds ratios (OR) with 95% confidence intervals [CI] of 'delay' in (not meeting) 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 performance[c]				
0–2	1016 (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]
P for trend			0.078	0.16
Attention[d]				
0–2	3731 (18.1)	1.00	1.00 reference	1.00 reference
3–5	1872 (19.4)	1.09	1.09 [1.02, 1.15]	1.06 [1.00, 1.13]
6–12	1404 (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]
P 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]
P for trend			0.010	0.004

[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 performance: at least 4 out of 5 milestones.
[d]Attention: 1 milestone.
[e]Cognitive/language skills: at least 3 out of 6 milestones.

Discussion

Overall, children of infertile couples reached developmental milestones similar to those for children of fertile couples at around 18 months of age. However, TTP 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 rate for the interview assessing developmental milestones across all groups of mothers, and non-responses were mainly due to unsuccessful attempts 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 the 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 $\leq$ 12 months (data not shown).

We had the opportunity to adjust for several covariates in the analyses. The effects of those factors on developmental milestones that 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 paediatricians' 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 to have 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- to 8-year-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 is likely to occur during natural fertilisation.

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 TTP 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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