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RESEARCH

Fertility treatment and risk of childhood and adolescent mental disorders: register based cohort study


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Abstract

Objective To assess the mental health of children born after fertility treatment by comparing their risk of mental disorders with that of spontaneously conceived children.

Design Prospective register based cohort study.

Setting Nationwide register based information from Danish National Health Registers cross linked by a unique personal identification number assigned to all citizens in Denmark.

Participants All children born in Denmark in 1995-2003 with follow-up in 2012 when the children were aged 8-17; 33 139 children were conceived after fertility treatment and 555 828 children were born after spontaneous conception.

Main outcome measures Absolute risks and hazard ratios for overall and specific mental disorders estimated with adjustment for potential confounding variables. Estimated association between the risk of mental disorders and subtypes of procedures, hormone treatments, gamete types, and cause of infertility.

Results The risk of mental disorders in children born after in vitro fertilisation or intracytoplasmic sperm injection was low, and was no higher than in spontaneously conceived children, except for a borderline significant increased risk of tic disorders (hazard ratio 1.40, 95% confidence interval 1.01 to 1.95; absolute risk 0.3%). In contrast, children born after ovulation induction with or without insemination had low but significantly increased risks of any mental disorder (1.20, 1.11 to 1.31; absolute risk 4.1%), autism spectrum disorders (1.20, 1.05 to 1.37; 1.5%), hyperkinetic disorders (1.23, 1.08 to 1.40; 1.7%), conduct, emotional, or social disorder (1.21, 1.02 to 1.45; 0.8%), and tic disorders (1.51, 1.16 to 1.96; 0.4%). There was no risk systematically related to any specific type of hormone drug treatment.

Conclusions There was a small increase in the incidence of mental disorders in children born after ovulation induction/intrauterine insemination. Children born after in vitro fertilisation/intracytoplasmic sperm injection were found to have overall risk comparable with children conceived spontaneously.

Introduction

Assisted reproduction techniques, induced ovulation, and intrauterine insemination are now widely used in the treatment of infertility, and in some countries children conceived after any medical assistance constitute up to 9% of newborns.[1] While over five million children have been born after assisted reproduction,[2] concerns are still being raised about potential adverse effects related to these procedures.[3]

Results from long term follow-up are sparse and inconsistent. Associations with behavioural or socioemotional development,[4] cognitive development,[5] psychomotor development,[6] or risk of mental disorders such as attention-deficit/hyperactivity disorder (ADHD)[7] have been observed in some but not all studies.[8 9] Furthermore, few studies have included children born after induced ovulation.[10]

We conducted a cohort study to investigate whether children conceived after fertility treatments have a higher, comparable, or lower risk of mental disorders in childhood or adolescence compared with children born after spontaneous conception. The study was based on a long term national register based follow-up in a large unselected cohort of children born after fertility treatments and aimed to overcome some limitations of previous studies regarding study size, follow-up time, and risk of bias.

Methods

Design and population

We designed a historic cohort study with prospective follow-up of all children born in Denmark from 1 January 1995 to 31 December 2003. Using the unique personal identification number, we established the cohort based on data from the Danish

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Medical Birth Register,[11] which includes all children born in Denmark. The personal identification number is assigned to all liveborn children in Denmark and can be used in research to ensure accurate individual level linkage between all national registers.

Information on fertility treatment

Fertility treatment was divided into two groups: in vitro fertilisation/intracytoplasmic sperm injection (IVF/ICSI) and hormone treatments for induced ovulation or intrauterine insemination). We assessed exposure to IVF and ICSI through the Danish IVF register,[12] which registers information from all public and private fertility clinics. It is mandatory by law to report all initiated treatments to the register. The register contains information on each woman's personal identification number, underlying cause of infertility, type of treatment (IVF, ICSI, fresh/frozen embryo, egg or semen donation), and type of drugs used, as well as information on pregnancy outcomes and the personal identification number of the resulting children since the start of the register in 1994. Information about exposure to hormones used for induced ovulation or intrauterine insemination was obtained from the Danish National Prescription Register,[13] which contains individual level data on all redeemed prescription drugs sold at outpatients pharmacies including date of dispensing, drug name, and dose units. We identified women who redeemed prescriptions on all types of drugs used for induced ovulation or intrauterine insemination based on a prespecified list (available from the authors). As these drugs can be prescribed for up to three months at a time we included women who redeemed the prescription at a date within 12 weeks before and four weeks after their last menstrual period. As the same drugs can also be used for IVF/ICSI we excluded any women in the IVF register with the same date of last menstrual period.

Mental disorders

Information on diagnoses of mental disorders was obtained from the Danish Psychiatric Central Research Register,[14] which contains individual level data on all admissions and outpatient contacts, including diagnoses and dates. Since 1994 diagnoses have been registered according to the international classification of diseases. According to ICD-10 and based on Classification of Mental and Behavioral Disorders we analysed the following outcome variables of mental disorders in childhood or adolescence: any mental disorder (F70.0-F99.9); any mental retardation and degrees of mental retardation (F70.0-F79.9); developmental disorders, all (F80.0-F89.9); developmental disorders of speech and language (F80x); scholastic skills (reading, spelling or calculating disorders) (F81x) or motor function (F82x); developmental disorders, mixed (F83x), pervasive developmental disorders (autism spectrum disorders) (F84x); developmental disorders, other (F88.0-F89.9); behavioural and emotional disorders, all (F90.0-F98.8); hyperkinetic disorder (F90x); conduct, emotional or social disorder (F91.0-F94.9); tic disorders (F950-F95.9); behavioural and emotional disorders, other (F98.8), and mental disorders, other (F99x). As few children were diagnosed with profound mental retardation we combined this category with severe mental retardation. We included both primary and supplementary diagnoses.

Covariates

We obtained information on important covariates, including maternal age, parity, educational level, smoking during pregnancy, child sex, birth weight, gestational age, multiplicity, Apgar score, and death or emigration, from the Medical Birth Register[11] and Statistics Denmark.[15] Information on maternal psychiatric history was obtained from the Danish Psychiatric Central Research Register.

Statistical analysis

All statistical analyses were based on an a priori specified analysis plan and performed with Stata/SE 12.[16] Each child contributed with time at risk beginning on the day of birth and ending on the earliest of either diagnosis, death, emigration, or end of follow-up on 16 February 2012. The date of diagnosis was considered as the earliest date a child received the first diagnosis (any mental disorder) or the date a child received the specific diagnosis relevant for the outcome in question. We estimated the risk of mental disorders associated with method of conception using standard Cox regression analyses. To account for correlations between siblings, all analyses were made with robust standard errors. Furthermore, we estimated the association between subtypes of procedures, hormone treatment, embryo types, and cause of infertility with the risk of mental disorders. In all analyses we adjusted for a priori determined possible confounding variables including maternal age (continuous), parity (primiparous/multiparous), smoking in pregnancy (yes/no), educational level (five groups), psychiatric history (yes/no), multiplicity (singleton/multiple), sex of child (male/female), and year of birth (three groups). Birth weight and gestational age were considered potential intermediate factors and were not included in the regression model. We made additional analyses stratifying for multiplicity and child's sex as well as restricting analyses to infant survivors (surviving >12 months) to reduce risk of survival bias.

We evaluated the proportional hazards assumption by graphical assessment of log-log plots and the assumption was met. In reporting the results we refer to the risks as hazard ratios with 95% confidence intervals. P values less than 0.05 were considered significant.

As all women who received fertility treatment were aged over 20, only children of mothers above this age were included in the study.

Results

A total of 599 126 children were born alive in Denmark from 1 January 1995 to 31 December 2003. We excluded 10 159 children born to mothers aged under 20, leaving 588 967 children in the study. Of these, 555 828 were born after spontaneous conception and 33 139 were conceived after any type of fertility treatment (14 991 born after IVF/ICSI and 18 148 after induced ovulation/intrauterine insemination).

Tables 1 and 2 show baseline characteristics of children and mothers according to conception methods.⇓⇓ At the end of follow-up the age of the children ranged from 8.1 to 17.1 (mean 12.7, SD 2.6), and 23 278 children (4%) has received a diagnosis of one or more of the included mental disorders. The absolute risk was 3.9% among children born after spontaneous conception, 3.5% in IVF/ICSI children, and 4.1% in children born after induced ovulation/intrauterine insemination. The proportion of children with a diagnosis of any mental disorder was significantly higher among boys (5.8%) than among girls (2.1%) (P<0.001). The mean age at the time of any diagnosis was 9.3 (SD 3.4, range 8 days-17 years).

Hazards associated with conception methods

Compared with children born after spontaneous conception, children born after IVF or ICSI had a higher hazard of tic disorders (hazard ratio 1.41, 95% confidence interval 1.05 to 1.87; absolute risk 0.3%) (table 3).⇓ This difference remained significant after adjustment for potential confounding variables (1.40, 1.01 to 1.95) and after restriction of analyses to infant survivors (1.40, 1.01 to 1.94). When we stratified analyses for multiplicity or sex of the child, the hazard ratio for tic disorders was not significantly increased. There were no other significant crude or adjusted hazard ratios of mental disorder in children or adolescents born after IVF/ICSI and spontaneously conceived controls.

Children conceived after induced ovulation/intrauterine insemination had significantly increased hazard ratio for any mental disorder in both crude (hazard ratio 1.15, 95% confidence interval 1.07 to 1.24) and adjusted analyses (1.20, 1.11 to 1.31; absolute risk 4.1%; table 4).⇓ The increased hazards were significant for both singletons, multiples, boys, girls, and infant survivors. When we examined categories of mental disorders, induced ovulation/intrauterine insemination was not associated with an increased hazard ratio for mental retardation or unspecified mental disorders but was systematically related to disorders of psychological development (1.17, 1.05 to 1.31; 2.2%) as well as behavioural and emotional disorders (1.22, 1.11 to 1.35; 2.8%). Within these categories the increased hazard ratio was primarily confined to autism spectrum disorders, hyperkinetic disorder, tic disorders and conduct, and emotional or social disorders. After stratification, we found that the increased hazard ratios for mental disorders within these categories were more consistent in boys than in girls, in whom they fell short of significance for hyperkinetic disorder, tic disorders, and conduct, emotional, or social disorders. Stratification for sex of the child did not show any significant differences in estimates between boys and girls, and thus no effect modification was present.

In general, the hazard estimates were systematically increased when we adjusted for maternal age, educational level, smoking in pregnancy, or psychiatric history. This increase in estimates ranged from 3% (developmental disorders) to a maximum of 24% (conduct, emotional, or social disorders) (detailed analyses available from the authors). Adjustment for all other variables reduced or did not change the estimates.

Hazards associated with type of treatment and cause of infertility

Apart from conception after induced ovulation/intrauterine insemination there were no systematic associations with type of treatment nor when we looked at children conceived after IVF and ICSI as separate groups (table 5).⇓ Similarly, there were no associations with the reported cause of infertility (available only for IVF/ICSI group).

Hazards associated with type of specific hormones and type of gamete or embryo

Information on type of hormonal treatment was available for all mothers in the induced ovulation/intrauterine insemination group and 51% of the mothers in the IVF/ICSI group. Some 8335 mothers were treated with a single type of hormonal drug. We found no association between treatment with clomiphene citrate, human chorionic gonadotrophin (hCG), or gonadotrophin releasing hormone (GnRH) and the hazard of any mental disorders, but there was an increased hazard ratio for any mental disorder after treatment with follicle stimulating hormone, although this was not significant within any category of mental disorders.

Information on type of embryo (fresh, frozen or donor egg, donor sperm) used for the conception was available for IVF/ICSI treatments. We found an increased hazard ratio for any mental disorder after IVF conception with donor sperm and hazard ratio of behavioural and emotional disorders after conception with donor oocyte but no significantly increased hazards associated with fresh or cryopreserved embryos.

Discussion

In this large long term follow-up of an unselected cohort of children conceived after fertility treatment, we found a systematically small increased risk of mental disorders in children born after induced ovulation/intrauterine insemination compared with spontaneously conceived children. When we considered the diagnoses in categories of mental disorders, there was a significant increased risk of autistic spectrum disorders, hyperkinetic disorders, tic disorders, and conduct, emotional, or social disorders. In contrast, beside a borderline significantly increased risk of tic disorders, we found no association between conception after IVF/ICSI and risk of mental disorders in childhood or adolescence. There were no systematic associations between cryopreserved embryos or gametes, types of hormones, or cause of infertility and risk of mental disorders.

Results in relation to other studies

Most studies investigating the neurodevelopment of children born after fertility treatment are small, with fewer than 500 participants and short term follow-up until the age of preschool or less (age 5).[10] These limitations are important as many neurodevelopmental deficits or mental disorders are diagnosed later in childhood.[17] Furthermore, several studies were unblinded to method of conception and unadjusted for potential confounders[10].

In line with our results, however, studies with follow-up beyond preschool age found no increased risk of problems in child behaviour[18 19] or socioemotional,[18 19] cognitive,[8 9] and psychomotor development[8] in children conceived after IVF or ICSI. Also, register based studies showed no association between conception after IVF/ICSI and development of mental disorders.[20 21]

In contrast, large register based studies from Sweden found increased risks of attention-deficit/hyperactivity disorder[7] and behavioural problems,[22] although significance was lost after adjustment for length of involuntary childlessness and restriction to term infants, respectively.

Few studies report long term neurodevelopmental follow-up of children born after induced ovulation. A previous shorter follow-up study investigating the risk of autism in our cohort found a significantly increased risk in girls born after induced ovulation.[23] In another Danish study the risk of developmental difficulties fell short of significance for all treatments, although induced ovulation carried the highest risk for behavioural problems.[24]

Contrary to our results, a population based sample from Finland showed increased risks of psychological, developmental, and emotional disorders after IVF/ICSI[25] but no association between these disorders and conception after induced ovulation, even though children born after induced ovulation showed poorer perinatal health and more episodes of long admission to hospital than the control children.[26] These studies included ICD-10 diagnoses from a hospital discharge register and child disability

allowance before the age of 2 but did not include outpatient contacts. As many psychological, developmental, and emotional disorders are diagnosed later in childhood, and often managed in outpatient clinics, this could explain the different findings. Furthermore, results from the United Kingdom's millennium cohort study showed no effect of either IVF/ICSI or induced ovulation on cognitive development of children up to age 5, but the number of exposed children was small.[27]

Strength and limitations

The strength of the present study lies in the large number of children born after IVF/ICSI and induced ovulation/intrauterine insemination and the long follow-up until late adolescence with adjustment for important confounding variables. The study is based on the Danish national health registers, thereby minimising the risk of selection bias.

For many outcomes, the hazard estimates increased after adjustment for potential confounders. This was lead by maternal age, educational level, smoking in pregnancy, and psychiatric history. Women seeking fertility treatment are generally different from other women giving birth with respect to socioeconomic position and health, which could reduce the risk of mental disorders in their offspring. Thus adjustment for such variables increased the association between fertility treatment and mental disorders, which has similarly been described previously.[22]

Although all analyses conducted were based on an a priori specified analysis plan, the numerous subgroup analyses in this study might lead to a risk of finding isolated significant associations because of chance alone. The significant associations in the main analyses, however, were systematically distributed with regard to both the exposure and the outcome. In contrast, the few isolated significant associations in the subanalyses were more likely to have been caused by chance.

Exposure to IVF or ICSI was assessed from the IVF register, and, although the coverage is believed to be close to 100% for the treatment reports, it might be less for the pregnancy outcome during the first years of the register.[12] Thus, a small portion of the IVF/ICSI children could be misclassified as spontaneously conceived, which would bias the estimates towards the null. But when we restricted our cohort to the 520 610 children born from 1996-2003, thus removing the first two years of the IVF register's activity, there were still no associations between IVF/ICSI and mental disorders (data not shown). Similarly, exposure to induced ovulation/intrauterine insemination was assessed from the prescription register, which contains complete information on all filled prescriptions[13] but no information as to whether the woman actually took the prescribed treatment. Thus, a small number of spontaneously conceived children could be misclassified as children born after induced ovulation/intrauterine insemination, which would lead to underestimated associations. But as the women are highly motivated to comply with treatment we believe the risk of bias is small. As exposure to both IVF/ICSI and induced ovulation/intrauterine insemination is based on Danish health registers, we included only children born after fertility treatment in Danish clinics. Denmark has a long tradition for free fertility treatment for infertile couples, and fertility tourism to other countries is primarily practiced by a small number of couples seeking egg donation (low availability in Denmark), simultaneous sperm and egg donation, or surrogacy (illegal in Denmark).

The Danish Psychiatric Central Research Register includes information on all people diagnosed with a given disorder but includes only cases with admissions or outpatient contacts. Previous studies have shown that children born after IVF or induced ovulation are more frequent users of hospital care compared with spontaneously conceived children.[22 26] Whether this is driven by poorer health outcomes related to the fertility treatment or the underlying subfertility or by general concerns about the health of these children is still debatable.[22 26] It might, however, lead to a risk of detection bias and thus overestimation of any association between fertility treatment and hospital diagnoses. Previous studies have not investigated differences in the use of the healthcare system between children born after IVF/ICSI or induced ovulation/intrauterine insemination. As we found increased hazard estimates after induced ovulation/intrauterine insemination but not after IVF/ICSI, we do not consider such differences a plausible explanation of our findings.

Any adverse perinatal or long term health outcomes in children born after fertility treatment might reflect the higher risk of multiplicity after these treatments. We accounted for this by stratifying our results for multiplicity, which did not alter the conclusions. We acknowledge the fact that even singletons born after assisted reproduction have an increased risk of preterm delivery,[28] but if this explained our results we would expect to find the same risk associated with IVF/ICSI treatments as we find for children born after induced ovulation. To clarify this further we conducted subanalyses restricted to infants born after 37 weeks' gestation. This did not alter our conclusions (data not shown).

Women with attention-deficit/hyperactivity disorder or other neuropsychiatric illnesses might be more likely to have an unplanned pregnancy outside a stable relationship, which would affect the probability of the child developing similar pathology for genetic reasons. This was the case in a Swedish study in which an association with attention-deficit/hyperactivity disorder among children born after IVF/ICSI did not become significant until the analysis was restricted to cohabiting women.[7] Unfortunately we did not have access to data regarding cohabitation status at the time of conception. This potential source of bias would only attenuate our estimates, but we believe that this risk is small in this study. Among other things, the analyses were adjusted for maternal history of psychiatric disorders as well as for maternal education and smoking in pregnancy. The analyses were not adjusted for parental factors (such as age and education). We also did not adjust for place of living or ethnicity of the family. There might be regional or cultural differences in the frequency of seeking medical advice for both fertility treatment and mental problems, which could have affected our results. We did, however, adjust the analyses for maternal education, which is likely to be associated with these variables, and the number of immigrants in Denmark is relatively low. Most importantly, if any of the above mentioned potential sources of confounding explained the results, we would expect the associations to be similar for both the IVF/ICSI and induced ovulation/intrauterine insemination groups. As we consistently found increased hazards for children born after induced ovulation/intrauterine insemination but not after IVF/ICSI, we believe that these potential sources of residual confounding probably did not cause systematic bias in our study. We cannot, however, be sure that other sources of residual confounding do not partly explain our results.

Our information on maternal psychiatric history was based on information from the Danish Psychiatric Central Research Register, which registers only disorders that required contact with the psychiatric healthcare system. Thus we do not have information on less severe cases of mental disorders in the mothers. As mental disorders run in families,[29] this could explain

our findings if children conceived after induced ovulation/intrauterine insemination were born to parents with a higher prevalence of mental disorders. This would be true if the conditions leading to infertility in the induced ovulation/intrauterine insemination group were associated with mental disorders or if couples with mental disorders had a higher risk of infertility. The recommended first line medical treatment for women with polycystic ovary syndrome is induced ovulation,[30] and these women have increased risk of mental disorders.[31] Furthermore, women with mental disorders might take longer to conceive,[32] which could lead to low tech fertility treatment such as induced ovulation, even though these couples do not have any history or reasons for infertility. In any case, the increased risk could be because of underlying parental factors and not the fertility treatment.

Recently, several studies have suggested that adverse effects associated with fertility treatment are related to the underlying subfertility rather than the procedures.[3 24] It is now a generally accepted hypothesis that subfertility per se has an important role in adverse effects in singletons born after medically assisted reproduction, although studies indicate that it is not the only contributor.[33] We believe our results support these previous findings. While IVF/ICSI is more complex than induced ovulation/intrauterine insemination and includes both hormonal stimulation and in vitro manipulation of gametes, we found no relation with IVF/ICSI but instead an association with induced ovulation/intrauterine insemination, which includes hormonal treatment alone. Hormonal stimulation is used in most fertility treatments and among induced ovulation and IVF/ICSI; the specific hormonal treatments differ mainly by the use of clomiphene citrate in induced ovulation.[34] As we found no evidence of an association with the use of this treatment, we believe that the reasons for the increased risk probably do not originate from the treatments but rather from the underlying causes of parental infertility among the parents in the induced ovulation/intrauterine insemination group.

As reported in other studies we found no differences on the long term neurodevelopment of children born after IVF or ICSI compared with spontaneously conceived children. We investigated the risks of hospital diagnoses but cannot eliminate the possibility that these children might develop minor or other deficits than the ones examined in this study. Our results, however, contribute to the evidence that the widely used IVF/ICSI techniques are safe for the developing offspring.

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Ethical approval: The study was approved by the Danish Data Protection Agency (File No 2012-41-1045). Register based studies do not require approval from ethics committees in Denmark.

Data sharing: Statistical code is available from the corresponding author.

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What is already known on this topic

- Children born after fertility treatment have an increased risk of some perinatal outcomes such as low birth weight, shorter gestational age, and congenital malformations
- The risk of malformations is related to the subfertility rather than the procedures or treatments
- Long term development is sparsely investigated and few have studied children born after induced ovulation

What this study adds

- The overall long term development of children born after IVF/ICSI is comparable with that of children conceived spontaneously
- Children born after induced ovulation seem to have a small increased risk of autism, hyperkinetic disorders, conduct, emotional or social disorder, and tic disorders, but the absolute risks are low

Tables

Table 1| Characteristics of children conceived after in vitro fertilisation/intracytoplasmic sperm injection (IVF/ICSI) and ovulation induction/intrauterine insemination (OI/IUI) or spontaneous conception in Denmark, 1995-2003. Figures are numbers (percentage) unless stated otherwise

	IVF/ICSI (n=14 991)	OI/IUI (n=18 148)	Spontaneous conception (n=555 828)
Male	7882 (52.6)	9387 (51.7)	285 226 (51.3)
Female	7109 (47.4)	8761 (48.3)	270 602 (48.7)
Age (years) at end of follow-up:			
8-12	9213 (61.5)	10 867 (59.9)	278 244 (50.2)
13-18	5106 (34.1)	6523 (35.9)	247 005 (44.4)
Dead or emigrated	672 (4.9)	758 (4.2)	29 979 (5.4)
Gestational age (weeks) at birth:			
<28	278 (1.9)	119 (0.66)	1247 (0.23)
28-31	529 (3.6)	339 (1.9)	3275 (0.59)
32-36	3108 (20.9)	2069 (11.4)	26 319 (4.8)
37-41	10 613 (71.2)	14 269 (78.6)	474 346 (85.9)
≥42	377 (2.5)	1351 (7.4)	46 745 (8.5)
Mean (SD) birth weight (g)	2985 (790)	3307 (741)	3515 (591)
Caesarean section:			
Yes	5092 (34.0)	4577 (25.2)	66 341 (11.9)
No	9899 (66.0)	13 571 (74.8)	489 487 (88.1)
Apgar score at 5 minutes (1-10):			
<7	236 (1.6)	242 (1.4)	5065 (0.92)
7-9	1524 (10.4)	1597 (8.9)	37 100 (6.8)
10	12 905 (88.0)	16 061 (89.7)	507 039 (92.3)
Multiplicity:			
Singleton	8501 (56.8)	14 982 (82.6)	541 616 (97.5)
Multiple	6478 (43.3)	3154 (17.4)	13 595 (2.5)

Table 2| Maternal characteristics according to conception after vitro fertilisation/intracytoplasmic sperm injection (IVF/ICSI) and ovulation induction/intrauterine insemination (OI/IUI) or spontaneous conception in Denmark, 1995-2003. Figures are numbers (percentage) unless stated otherwise

	IVF/ICSI (n=14 991)	OI/IUI (n=18 148)	Spontaneous conception (n=555 828)
Mean (SD) age (years)	33.3 (3.9)	31.7 (4.3)	29.9 (4.6)
Parity:			
Primiparous	11 099 (74.0)	11 072 (61.0)	228 059 (41.0)
Multiparous	3892 (26.0)	7076 (39.0)	327 746 (59.0)
Smoking in pregnancy:			
Yes	2631 (17.6)	2755 (15.2)	123 512 (22.3)
No	12 293 (82.4)	15 377 (84.8)	429 728 (77.7)
Educational level:			
Primary school	2175 (17.5)	2466 (16.1)	111 404 (23.1)
Secondary school	967 (7.8)	1495 (9.7)	56 294 (11.7)
Short cycle higher education (+2-3 years)	5495 (44.3)	6687 (43.6)	193 260 (40.0)
Medium cycle higher education (+3-5 years)	2513 (20.3)	3030 (19.7)	82 188 (17.0)
Long cycle higher education (+ ≥5 years)	1261 (10.2)	1689 (10.9)	39 663 (8.2)
Any psychiatric history/disorder	1240 (8.3)	1663 (9.2)	58 704 (10.6)

Table 3| Hazard ratios and 95% confidence intervals for mental disorders* in 14 991children aged 0-17 born after in vitro fertilisation/intracytoplasmic sperm injection (IVF/ICSI) compared with 558 828 spontaneously conceived children

	Absolute risk (%)		Hazard ratio in IVF/ICSI children						
	Spontaneous conception	IVF/ICSI	Crude	Adjusted†	Singletons‡	Multiples‡	Boys§	Girls§	Infant survivors†¶
Any mental disorder	22 009 (3.9)	524 (3.5)	0.99 (0.90 to 1.08)	1.04 (0.94 to 1.15)	1.04 (0.92 to 1.17)	1.08 (0.86 to 1.34)	1.05 (0.94 to 1.18)	0.99 (0.79 to 1.22)	1.04 (0.94 to 1.15)
Mental retardation:									
Any	3217 (0.6)	65 (0.4)	0.82 (0.64 to 1.06)	0.84 (0.63 to 1.12)	0.89 (0.62 to 1.27)	0.83 (0.48 to 1.43)	0.86 (0.63 to 1.19)	0.77 (0.42 to 1.40)	0.84 (0.63 to 1.12)
Mild	1910 (0.3)	36 (0.2)	0.77 (0.55 to 1.08)	0.76 (0.51 to 1.13)	0.98 (0.63 to 1.54)	0.64 (0.30 to 1.34)	0.76 (0.48 to 1.18)	0.75 (0.33 to 1.69)	0.76 (0.51 to 1.13)
Moderate	610 (0.1)	18 (0.1)	1.21 (0.76 to 1.93)	1.29 (0.80 to 2.10)	0.62 (0.23 to 1.68)	1.59 (0.60 to 4.22)	1.22 (0.72 to 2.06)	1.47 (0.48 to 4.49)	1.29 (0.80 to 2.10)
Severe to profound	145 (0.03)	2 (0.01)	0.55 (0.14 to 2.20)	0.52 (0.14 to 1.94)	0.44 (0.06 to 3.21)	0.77 (0.03 to 17.5)	1.25 (0.33 to 4.69)	NA	0.52 (0.14 to 1.94)
Other or unspecified	552 (0.1)	9 (0.06)	0.65 (0.31 to 1.34)	0.73 (0.31 to 1.70)	1.03 (0.46 to 2.32)	0.38 (0.03 to 5.27)	0.75 (0.30 to 1.85)	0.70 (0.15 to 3.21)	0.73 (0.31 to 1.70)
Disorders of psychological development:									
Any	11 099 (2,0)	292 (1.9)	1.08 (0.96 to 1.21)	1.02 (0.89 to 1.17)	1.05 (0.89 to 1.23)	1.03 (0.78 to 1.37)	1.05 (0.90 to 1.22)	0.90 (0.65 to 1.25)	1.02 (0.89 to 1.17)
Speech and language	1568 (0.3)	29 (0.2)	0.72 (0.49 to 1.05)	0.78 (0.49 to 1.24)	1.05 (0.65 to 1.70)	0.33 (0.12 to 0.93)	0.76 (0.46 to 1.27)	0.84 (0.31 to 2.28)	0.78 (0.49 to 1.24)
Scholastic skills	709 (0.1)	14 (0.1)	0.88 (0.52 to 1.49)	0.95 (0.54 to 1.68)	0.90 (0.42 to 1.92)	1.38 (0.51 to 3.71)	0.96 (0.49 to 1.86)	0.91 (0.30 to 2.78)	0.95 (0.54 to 1.68)
Motor function	587 (0.1)	16 0.1)	1.06 (0.63 to 1.80)	1.01 (0.57 to 1.81)	0.94 (0.46 to 1.93)	1.09 (0.34 to 3.54)	0.96 (0.52 to 1.78)	1.30 (0.32 to 5.32)	1.01 (0.57 to 1.81)
Mixed	1989 0.4)	50 (0.3)	1.05 (0.79 to 1.39)	1.08 (0.77 to 1.51)	1.28 (0.87 to 1.88)	0.65 (0.34 to 1.21)	1.06 (0.73 to 1.54)	1.18 (0.55 to 2.54)	1.08 (0.77 to 1.51)
Autism spectrum disorders	7060 (1.3)	197 (1.3)	1.14 (0.99 to 1.31)	1.02 (0.87 to 1.20)	0.95 (0.77 to 1.16)	1.42 (0.99 to 2.04)	1.07 (0.90 to 1.28)	0.85 (0.57 to 1.27)	1.03 (0.87 to 1.21)
Other or unspecified	940 (0.2)	29 (0.2)	1.25 (0.85 to 1.83)	1.04 (0.66 to 1.65)	1.31 (0.81 to 2.10)	0.81 (0.31 to 2.14)	1.14 (0.69 to 1.90)	0.71 (0.24 to 2.09)	1.04 (0.66 to 1.65)
Behavioural and emotional disorders:									
Any	15 563 (2.8)	360 (2.4)	0.96 (0.86 to 1.07)	1.08 (0.95 to 1.22)	1.05 (0.90 to 1.22)	1.12 (0.86 to 1.46)	1.07 (0.93 to 1.23)	1.07 (0.84 to 1.39)	1.08 (0.95 to 1.22)
Hyperkinetic disorder (ADHD)	9252 (1.7)	203 (1.4)	0.92 (0.79 to 1.06)	1.01 (0.86 to 1.19)	0.97 (0.79 to 1.19)	1.07 (0.75 to 1.51)	1.03 (0.86 to 1.23)	0.90 (0.60 to 1.34)	1.01 (0.86 to 1.19)
Conduct, emotional or social disorders	4836 (0.9)	99 (0.7)	0.84 (0.69 to 1.03)	1.09 (0.87 to 1.36)	1.09 (0.84 to 1.44)	1.12 (0.68 to 1.83)	1.06 (0.81 to 1.39)	1.14 (0.75 to 1.73)	1.09 (0.87 to 1.37)
Tic disorders	1424 (0.3)	48 (0.3)	1.41 (1.05 to 1.87)	1.40 (1.01 to 1.95)	1.46 (0.99 to 2.17)	1.61 (0.82 to 3.16)	1.34 (0.94 to 1.90)	1.84 (0.79 to 4.30)	1.40 (1.01 to 1.94)
Other	3424 (0.6)	78 (0.5)	0.95 (0.76 to 1.20)	1.00 (0.77 to 1.29)	0.91 (0.66 to 1.27)	0.97 (0.56 to 1.66)	0.93 (0.68 to 1.27)	1.18 (0.76 to 1.82)	1.00 (0.77 to 1.29)
Unspecified mental disorder	647 (0.1)	13 (0.1)	0.86 (0.48 to 1.56)	0.93 (0.48 to 1.77)	1.26 (0.67 to 2.38)	0.62 (0.13 to 3.09)	0.86 (0.39 to 1.90)	1.02 (0.38 to 2.75)	0.93 (0.48 to 1.77)

NA=not applicable.

*As defined by ICD-10 (applicable in study period).

†Adjusted for maternal age, parity, educational level, smoking in pregnancy, maternal psychiatric history, birth year, child's sex, and multiplicity.

‡Adjusted for maternal age, parity, educational level, smoking in pregnancy, maternal psychiatric history, birth year, and child's sex.

§Adjusted for maternal age, parity, educational level, smoking in pregnancy, maternal psychiatric history, birth year, and multiplicity.

¶Children surviving first year of life.

Table 4| Hazard ratios and 95% confidence intervals for mental disorders* in 18 148 children aged 0-17 born after ovulation induction with or without intrauterine insemination (OI/IUI) compared with 558 828 spontaneously conceived children

	Absolute risk (%)		Hazard ratio in OI/IUI children						
	Spontaneous conception	OI/IUI	Crude	Adjusted†	Singletons‡	Multiples‡	Boys§	Girls§	Infant survivors†¶
Any mental disorder	22 009 (3.9)	745 (4.1)	1.15 (1.07 to 1.24)	1.20 (1.11 to 1.31)	1.18 (1.08 to 1.29)	1.36 (1.06 to 1.74)	1.18 (1.08 to 1.30)	1.29 (1.10 to 1.51)	1.20 (1.11 to 1.31)
Mental retardation:									
Any	3217 (0.6)	89 (0.5)	0.92 (0.74 to 1.14)	1.02 (0.81 to 1.28)	1.00 (0.77 to 1.29)	1.13 (0.65 to 1.98)	0.93 (0.71 to 1.22)	1.27 (0.85 to 1.88)	1.02 (0.81 to 1.28)
Mild	1910 (0.3)	47 (0.3)	0.82 (0.62 to 1.10)	0.94 (0.69 to 1.27)	0.85 (0.60 to 1.21)	1.43 (0.75 to 2.72)	0.89 (0.63 to 1.28)	1.06 (0.60 to 1.88)	0.94 (0.69 to 1.27)
Moderate	610 (0.1)	19 (0.1)	1.04 (0.66 to 1.64)	1.11 (0.68 to 1.83)	1.15 (0.68 to 1.97)	0.97 (0.23 to 4.04)	0.97 (0.52 to 1.79)	1.52 (0.67 to 3.44)	1.11 (0.68 to 1.83)
Severe to profound	145 (0.03)	2 (0.01)	0.45 (0.11 to 1.80)	0.46 (0.12 to 1.85)	0.27 (0.04 to 1.95)	1.78 (0.18 to 18.1)	0.42 (0.06 to 3.00)	0.49 (0.07 to 3.19)	0.46 (0.12 to 1.85)
Other or Unspecified	552 (0.1)	21 (0.1)	1.24 (0.80 to 1.93)	1.38 (0.84 to 2.25)	1.59 (0.98 to 2.60)	0.40 (0.05 to 2.97)	1.14 (0.61 to 2.12)	2.05 (0.91 to 4.63)	1.38 (0.84 to 2.25)
Disorders of psychological development:									
Any	11 099 (2.0)	403 (2.2)	1.21 (1.10 to 1.34)	1.17 (1.05 to 1.31)	1.13 (1.00 to 1.27)	1.46 (1.07 to 1.99)	1.15 (1.02 to 1.30)	1.25 (0.99 to 1.58)	1.17 (1.05 to 1.31)
Speech and language	1568 (0.3)	53 (0.3)	1.07 (0.82 to 1.41)	1.14 (0.84 to 1.55)	1.13 (0.81 to 1.57)	0.99 (0.45 to 2.16)	1.15 (0.82 to 1.62)	1.12 (0.56 to 2.21)	1.14 (0.84 to 1.55)
Scholastic skills	709 (0.1)	17 (0.1)	0.86 (0.53 to 1.40)	0.94 (0.58 to 1.51)	0.74 (0.41 to 1.34)	2.34 (0.92 to 5.92)	1.05 (0.62 to 1.76)	0.63 (0.20 to 2.06)	0.94 (0.58 to 1.51)
Motor function	587 (0.1)	10 (0.1)	0.54 (0.29 to 1.01)	0.52 (0.27 to 1.02)	0.55 (0.27 to 1.11)	0.34 (0.05 to 2.40)	0.48 (0.23 to 1.01)	0.76 (0.17 to 3.37)	0.52 (0.27 to 1.02)
Mixed	1989 (0.4)	69 (0.4)	1.18 (0.93 to 1.50)	1.25 (0.97 to 1.62)	1.35 (1.03 to 1.77)	0.69 (0.32 to 1.49)	1.33 (1.00 to 1.77)	0.95 (0.50 to 1.82)	1.25 (0.97 to 1.62)
Autism spectrum disorders	7060 (1.3)	272 (1.5)	1.29 (1.14 to 1.46)	1.20 (1.05 to 1.37)	1.15 (1.00 to 1.33)	1.73 (1.17 to 2.55)	1.16 (1.00 to 1.35)	1.36 (1.02 to 1.80)	1.20 (1.05 to 1.37)
Other or unspecified	940 (0.2)	37 (0.2)	1.30 (0.93 to 1.82)	1.11 (0.77 to 1.60)	0.95 (0.62 to 1.45)	2.11 (0.83 to 5.35)	1.12 (0.73 to 1.71)	1.08 (0.51 to 2.27)	1.11 (0.77 to 1.60)
Behavioural and emotional disorders:									
Any	15 563 (2.8)	509 (2.8)	1.11 (1.02 to 1.22)	1.22 (1.11 to 1.35)	1.21 (1.10 to 1.34)	1.27 (0.95 to 1.70)	1.20 (1.07 to 1.34)	1.30 (1.07 to 1.58)	1.22 (1.11 to 1.35)
Hyperkinetic disorder (ADHD)	9252 (1.7)	306 (1.7)	1.13 (1.00 to 1.27)	1.23 (1.08 to 1.40)	1.21 (1.05 to 1.38)	1.38 (0.96 to 1.99)	1.22 (1.06 to 1.40)	1.29 (0.98 to 1.71)	1.23 (1.08 to 1.40)
Conduct, emotional or social disorders	4,836 (0.9)	143 (0.8)	0.99 (0.84 to 1.18)	1.21 (1.02 to 1.45)	1.21 (1.00 to 1.46)	1.25 (0.73 to 2.11)	1.23 (1.00 to 1.52)	1.20 (0.86 to 1.66)	1.22 (1.02 to 1.45)
Tic disorders	1424 (0.3)	64 (0.4)	1.52 (1.18 to 1.96)	1.51 (1.16 to 1.96)	1.32 (0.98 to 1.79)	2.75 (1.38 to 5.50)	1.62 (1.23 to 2.13)	0.86 (0.34 to 2.13)	1.51 (1.16 to 1.96)
Other	3,424 (0.6)	99 (0.5)	0.99 (0.81 to 1.21)	1.03 (0.83 to 1.28)	1.06 (0.85 to 1.33)	0.82 (0.42 to 1.59)	0.95 (0.74 to 1.24)	1.25 (0.85 to 1.82)	1.03 (0.83 to 1.28)
Unspecified mental disorder	647 (0.1)	22 (0.1)	1.22 (0.78 to 1.90)	1.16 (0.72 to 1.86)	1.02 (0.60 to 1.73)	1.95 (0.61 to 6.25)	1.14 (0.63 to 2.09)	1.18 (0.55 to 2.54)	1.16 (0.72 to 1.86)

*As defined by ICD-10 (applicable in study period).

†Adjusted for maternal age, parity, educational level, smoking in pregnancy, maternal psychiatric history, birth year, child's sex, and multiplicity.

‡Adjusted for maternal age, parity, educational level, smoking in pregnancy, maternal psychiatric history, birth year, and child's sex.

§Adjusted for maternal age, parity, educational level, smoking in pregnancy, maternal psychiatric history, birth year, and multiplicity.

¶Children surviving first year of life.

Table 5| Hazard rates and 95% confidence intervals for mental disorders*† in children aged 0-17 according to type of infertility treatment, hormones, gametes, and aetiology of infertility compared with spontaneously conceived children

	No of exposed	Any psychiatric diagnosis (n=23 278)	Mental retardation (n=3371)	Disorders of psychological development (n=11 794)	Behaviour and emotional disorders (n=16 432)	Other/unspecified psychiatric disorders (n=682)
Procedure‡:						
OI/IUI	18 148	1.20 (1.11 to 1.31)	1.02 (0.81 to 1.28)	1.17 (1.05 to 1.31)	1.22 (1.11 to 1.34)	1.16 (0.72 to 1.87)
IVF	9532	1.01 (0.90 to 1.15)	0.88 (0.63 to 1.24)	0.98 (0.83 to 1.15)	1.06 (0.91 to 1.23)	1.14 (0.56 to 2.29)
ICSI	4201	1.08 (0.90 to 1.31)	0.81 (0.47 to 1.42)	1.17 (0.92 to 1.49)	1.10 (0.87 to 1.38)	0.33 (0.05 to 2.45)
Hormone treatment§:						
Clomiphene citrate	5857	1.05 (0.92 to 1.21)	0.87 (0.59 to 1.31)	0.95 (0.78 to 1.15)	1.10 (0.94 to 1.29)	1.15 (0.55 to 2.42)
FSH	905	1.50 (1.07 to 2.10)	0.87 (0.28 to 2.71)	1.46 (0.94 to 2.26)	1.49 (0.98 to 2.26)	1.42 (0.20 to 9.97)
hCG	1422	1.02 (0.76 to 1.37)	0.78 (0.32 to 1.88)	0.76 (0.48 to 1.19)	1.07 (0.75 to 1.52)	2.70 (0.99 to 7.34)
GnRH agonist/antagonist	151	0.81 (0.30 to 2.18)	NA	0.34 (0.05 to 2.47)	0.95 (0.30 to 2.96)	NA
Type of gametes**:						
Fresh embryo	13 725	1.06 (0.95 to 1.18)	0.89 (0.66 to 1.20)	1.05 (0.91 to 1.21)	1.09 (0.96 to 1.24)	1.00 (0.51 to 1.98)
Frozen embryo	986	0.93 (0.64 to 1.35)	0.65 (0.21 to 2.00)	0.87 (0.53 to 1.45)	0.85 (0.54 to 1.36)	1.06 (0.15 to 7.61)
Donor oocyte	165	1.57 (0.82 to 3.02)	NA	1.77 (0.80 to 3.93)	2.18 (1.08 to 4.37)	NA
Donor sperm	606	1.56 (1.05 to 2.30)	1.83 (0.64 to 5.23)	1.53 (0.89 to 2.60)	1.42 (0.88 to 2.28)	NA
Aetiology¶:						
Male factor	4019	1.05 (0.87 to 1.289)	0.86 (0.49 to 1.53)	1.04 (0.80 to 1.34)	1.11 (0.87 to 1.40)	0.68 (0.17 to 2.81)
Ovulation factor	929	1.31 (0.91 to 1.89)	1.15 (0.43 to 3.09)	1.48 (0.95 to 2.31)	1.07 (0.65 to 1.78)	4.78 (1.13 to 20.2)
Tuba factor	4859	1.02 (0.87 to 1.20)	0.91 (0.58 to 1.41)	0.96 (0.77 to 1.19)	1.07 (0.89 to 1.30)	0.92 (0.35 to 2.38)
Mixed	5136	1.05 (0.89 to 1.25)	0.73 (0.44 to 1.19)	1.07 (0.86 to 1.34)	1.09 (0.89 to 1.34)	0.71 (0.22 to 2.34)

NA=not applicable (no cases among exposed).

OI/IUI=ovulation induction/intrauterine insemination, IVF=in vitro fertilisation, ICSI=intracytoplasmic sperm injection, FSH=follicle stimulating hormone, hCG=human chorionic gonadotrophin, GnRH=gonadotrophin releasing hormone.

*As defined by ICD-10 (applicable in study period).

†Adjusted for maternal age, parity, educational level, smoking in pregnancy, maternal psychiatric history, birth year, child's sex, and multiplicity.

‡Specific type of treatment missing in 117 children in IVF/ICSI group; 163 had egg donation and 978 were fertilised with frozen egg without specification of treatment type (IVF or ICSI).

§Treatment in mono-therapy; included only cases where no other than specific drug was used. Available from all in OI group and 51% in IVF/ICSI group.

¶Available for IVF/ICSI group only.