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Fertility Treatment and Childhood Epilepsy - a Nationwide Cohort Study of 565,166 Live Births

Laura Ozer Kettner, MD,

Perinatal Epidemiology Research Unit, Department of Paediatrics, Aarhus University Hospital, 8200 Aarhus, Denmark

Ulrik Schiøler Kesmodel [Professor],

The Fertility Clinic, Department of Obstetrics and Gynaecology, Herlev University Hospital, 2730 Herlev, Denmark

Cecilia Høst Ramlau-Hansen [Professor],

Department of Public Health, Section for Epidemiology, Aarhus University, 8000 Aarhus, Denmark

Bjørn Bay, PhD,

The fertility clinic, Aarhus University, Regions Hospital Horsens, 8700 Horsens, Denmark

Beate Ritz [Professor],

Department of Epidemiology, School of Public Health, University of California, 90095 Los Angeles, USA

Niels Bjerregaard Matthiesen, PhD, and

Corresponding author: Laura Ozer Kettner, Perinatal Epidemiology Research Unit, Department of Paediatrics, Aarhus University Hospital, Palle Juul-Jensens Blvd. 99, 8200 Aarhus N, Denmark, Laura@kettner.nu, phone: +45 61 66 45 45.

Author Contributions:

LOK, USK, CHR-H, BB and TBH contributed substantially to the conception and design of the study and the data acquisition. All authors contributed substantially to the analysis and interpretation of the data. LOK wrote the first draft for the manuscript, which was critically revised by all authors. All authors approved the final version and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. LOK is guarantor for the study.

Ethical approval

The study was approved by the State Serum Institute, Statistics Denmark and the Danish Data Protection Agency (reference 2014-41-2686). Studies based on Danish register data do not require approval from ethics committees.

Research integrity

LOK affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained. Furthermore, LOK affirms that the study hypothesis arose before inspection of the data. All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. Statistical codes are available from LOK upon reasonable request.

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Perinatal Epidemiology Research Unit, Department of Paediatrics, Aarhus University Hospital, 8200 Aarhus, Denmark

Tine Brink Henriksen [Professor]

Perinatal Epidemiology Research Unit, Department of Paediatrics, Aarhus University Hospital, 8200 Aarhus, Denmark

Abstract

Background—Fertility treatment includes hormonal stimulation of the woman and in vitro manipulation of gametes and embryos that may influence prenatal brain development. We aimed to investigate the association between fertility treatment and childhood epilepsy, including specific types of treatment and indications as well as subtypes of epilepsy.

Methods—In this nationwide birth cohort study, we included all pregnancies in Denmark resulting in live-born singletons, 1995–2003. Children conceived by fertility treatment and children developing epilepsy (until 2013) were identified from Danish national registers.

Results—A total of 565,116 pregnancies were included; 8,071 children (1.4%) developed epilepsy.

Children conceived after ovulation induction or intrauterine insemination had a slightly higher risk of childhood epilepsy (hazard ratio (HR) 1.15; 95% confidence interval (CI): 1.00 – 1.31). The association was more pronounced for the subtypes idiopathic generalized and focal epilepsy. Regarding the specific hormonal treatments, only clomiphene citrate was associated with an increased risk of childhood epilepsy, also in a sibling analysis (HR 2.07; 95% CI: 1.05 – 4.08).

In vitro fertilization or intracytoplasmic sperm injection was not associated with an overall increased risk of childhood epilepsy but with idiopathic generalized epilepsy (HR 1.43; 95% CI: 0.99 – 2.05). No clear associations were seen regarding other treatment types or indications.

Conclusions—Children conceived by ovulation induction or intrauterine insemination with clomiphene citrate may be at slightly increased risk of childhood epilepsy. Furthermore, children conceived by in vitro fertilization or intracytoplasmic sperm injection may be at slightly increased risk of idiopathic generalized epilepsy.

During the last three decades, the use of fertility treatment has increased¹. As the field strives for continuous improvement of the treatments, new technologies, medications, and procedures have been introduced. Reports from 2014 estimated that worldwide 350,000 children have been born as a result of in vitro fertilization (IVF) or intracytoplasmic sperm injection each year². Additionally, a large number of children were conceived by less invasive procedures, such as ovulation induction or intrauterine insemination³.

Fertility treatment bypasses natural conception by means of hormonal stimulation of the woman and mechanical and chemical manipulation of the gametes and the early embryo⁴. Hence, concerns have been raised about potentially negative consequences for the developing child. Although previous research has reported adverse pregnancy outcomes, even in singleton births⁵, studies investigating potential long-term health effects are sparse⁶.

Prenatal brain development is a highly complex process that may easily be disturbed, and exposures during crucial stages of development may result in disease or dysfunction later in life⁷. A few studies have suggested that fertility treatment may be associated with an increased risk of childhood epilepsy^{8,9}. However, it remains unknown whether this risk is related to the hormonal stimulation, the in vitro manipulation of gametes and embryos, or perhaps due to confounding by indication, i.e. factors contributing both to the underlying parental infertility¹⁰ and the development of childhood epilepsy. Additionally, it has not been studied whether fertility treatment is associated with an increased risk of specific types of epilepsy.

The aim of the present study was to investigate the association between fertility treatment and the development of childhood epilepsy within a large nationwide birth cohort using information from high-quality health registers. Additionally, we aimed to address the possible effects of specific treatments and indications as well as the risk of the development of specific types of childhood epilepsy.

Methods

Design and population

In this nationwide birth cohort study, we included all pregnancies in Denmark resulting in a live-born singleton child from 1 January 1995 to 31 December 2003. The study population was identified from the Danish Medical Birth Registry in which all children born in Denmark have been registered since 1973¹¹. Using the unique personal identification number assigned to all legal Danish residents, we linked individual-level information from the Danish Medical Birth Registry to information from the Danish IVF register¹², the Danish National Prescription Registry¹³, and the Danish National Patient Register¹⁴. Additionally, we obtained information on maternal education as well as emigration and vital status of the children from Statistics Denmark¹⁵.

Since the minimum age of mothers in the cohort who had received fertility treatment was 20 years, we excluded spontaneously conceived children born to mothers younger than 20 years.

Fertility treatment

IVF and intracytoplasmic sperm injection constitute the most invasive types of fertility treatment. Follicle-stimulating hormone and human chorionic gonadotropin are used to induce ovulation^{16,17}, after which oocytes are retrieved by transvaginal aspiration and fertilized in vitro. In the case of intracytoplasmic sperm injection, a single spermatozoon is injected into the oocyte⁴. Children conceived by IVF and intracytoplasmic sperm injection were identified from the Danish IVF register along with information about the treatment and the treatment indications. Since 1994, it has been mandatory for all public and private fertility clinics in Denmark to report each initiated IVF-cycle to the Danish IVF register¹².

Less invasive types of fertility treatment comprise ovulation induction with or without intrauterine insemination. One of the most frequently used hormones for ovulation induction is clomiphene citrate administered on days 3 to 7 of the menstrual cycle. Additional

hormone supplementation may also be required. If intrauterine insemination is performed, a concentrated sperm sample is introduced into the woman's uterine cavity at the time of ovulation⁴. Children conceived by ovulation induction or intrauterine insemination are not included in the Danish IVF register and were identified from the Danish National Prescription Registry from records of maternal hormonal treatment. Since 1995, all redeemed prescriptions in Denmark have been reported to the register according to the Anatomical Therapeutic Codes (ATC) for drugs along with the dispensing date¹³. The hormone prescriptions consistent with ovulation induction or intrauterine insemination treatment had to be redeemed within 12 weeks before to four weeks after the last menstrual period recorded in the Danish Medical Birth Registry. This time span was chosen since hormonal treatment may be prescribed for up to 12 weeks at a time. Pregnancies recorded in the Danish IVF register were not included in the ovulation induction or intrauterine insemination group. From the Danish national health registers, it is impossible to distinguish ovulation induction from intrauterine insemination and whether the infertility was due to maternal or paternal factors.

Epilepsy

Children developing epilepsy were identified from the Danish National Patient Register and from redeemed prescriptions in the Danish National Prescription Registry. The Danish National Patient Register holds information on all hospital contacts (in- and outpatient visits) in Denmark since 1995, including the date of the contact as well as physician-assigned diagnoses. The diagnoses are classified according to the International Classification of Diseases (ICD)¹⁴. We defined epilepsy as either a primary diagnosis of epilepsy or status epilepticus (ICD, 10th Edition (ICD-10): G40 or G41), or the redemption of at least two separate prescriptions for any antiepileptic drug (ATC: N03A or N05BA09¹⁸). Using both data sources ensured identification of children diagnosed with epilepsy at both private clinics and hospitals.

Statistical analyses

The analyses were performed in Stata 14 (StataCorp, TX, USA). All children were followed from the date of birth to the date of the first diagnosis of epilepsy or the first prescription for any antiepileptic drug, the date of emigration or death, or until the end of follow-up (31 December 2013), whichever occurred first. Cox proportional hazards regression was used to estimate hazard rate ratios (HRs) and 95% confidence intervals (CIs). The proportional hazards assumption was checked graphically using log-log plots and predicted survival plots. Robust standard errors were used to account for correlations between siblings in the cohort.

The following potential confounders, selected a priori on the basis of directed acyclic graphs¹⁹, were included in the analyses: maternal age at birth (continuous using fractional polynomials), maternal smoking during pregnancy (yes or no), maternal ethnicity (Western or non-Western)²⁰ ascertained from the Danish Medical Birth Registry, maternal education (five groups), maternal diagnosis of epilepsy in the Danish National Patient Register prior to birth (yes or no), and child's year of birth (1995–1997, 1998–2000, 2001–2003).

Missing data were imputed using multiple imputation under the assumption of data being missing at random²¹. The covariate containing the largest proportion of missing observations was maternal ethnicity (23%). Complete exposure and outcome information was available for all participants in the primary analyses (see eAppendix 1 for details regarding the multiple imputation).

We performed a number of subgroup analyses estimating 1) the risk of specific types of childhood epilepsy believed to be of genetic (idiopathic generalized epilepsy, ICD-10: G403) and structural origin (focal epilepsy, ICD-10: G401, G402)^{22–24} and 2) the risk associated with specific types of hormones used as monotherapy for ovulation induction or intrauterine insemination (clomiphene citrate, follicle-stimulating hormone, human chorionic gonadotropin). For IVF or intracytoplasmic sperm injection, we assessed the risk associated with 3) the specific procedure (IVF or intracytoplasmic sperm injection), 4) the type of gametes used (fresh embryo, frozen embryo, donated semen), and 5) the treatment indication (male factor, ovulation factor, tubal factor, other factor). Finally, the following sensitivity analyses were performed to test the robustness of our results: We applied a sibling design comparing siblings born to the same mother but discordant for exposure and outcome. By use of this approach, we accounted for potential confounding from genetic and family specific factors contributing to both the underlying parental infertility and the development of childhood epilepsy. These analyses were adjusted for maternal age at the index birth, smoking during pregnancy, and the child's year of birth. Secondly, the criterion for epilepsy was restricted to both a primary diagnosis of epilepsy as well as redemption of at least two prescriptions for antiepileptic drugs. In further analyses, children diagnosed with a chromosomal anomaly in the Danish National Patient Register were excluded, or children only receiving an epilepsy diagnosis or antiepileptic drugs before 28 days of life were excluded. Furthermore, the primary analyses were carried out as complete-case analyses. Finally, all analyses of IVF or intracytoplasmic sperm injection were adjusted for treatment indication.

Results

Maternal and infant characteristics of the 565,116 included pregnancies are presented in Table 1. As expected, the proportion of children conceived by fertility treatment increased over the study period. Women conceiving after fertility treatment tended to be older, more educated, more frequently primiparous, of Western origin, and less likely to smoke during pregnancy than women conceiving spontaneously. A slightly larger percentage of the ovulation induction- or intrauterine insemination-treated women had a history of epilepsy compared with women who conceived following IVF, intracytoplasmic sperm injection, or spontaneously.

During 7,844,119 person-years at risk, 8,071 children (1.4%) developed epilepsy; 2,699 children were identified only from the Danish National Patient Register, 1,275 children were identified only from the Danish National Prescription Registry, whereas 4,097 children were identified from both registers. A total of 1,574 children were diagnosed with idiopathic generalized epilepsy, and 1,732 children were diagnosed with focal epilepsy. The median

follow-up time was 14 years. During follow-up, 32,184 children (5.7%) were censored due to death or emigration.

Compared to spontaneously conceived children, the risk of epilepsy was slightly higher in children conceived after ovulation induction or intrauterine insemination (HR 1.15; 95% CI: 1.00 – 1.31) (Table 2). The association was more pronounced for specific subtypes of epilepsy; idiopathic generalized epilepsy and focal epilepsy (Table 3). With respect to hormonal treatment, only treatment with clomiphene citrate was associated with an increased risk of epilepsy (Table 4). This result was consistent using a sibling design (HR 2.07; 95% CI: 1.05 – 4.08).

IVF or intracytoplasmic sperm injection was not associated with an increased risk of childhood epilepsy (Table 2). However, when assessing the risk of specific subtypes of epilepsy, we saw an association with idiopathic generalized epilepsy (HR 1.43; 95% CI: 0.99 – 2.05) but not with focal epilepsy (Table 3). We observed no clear patterns of association regarding the type of procedure, the type of gamete, or the treatment indication (Table 4).

The association between ovulation induction or intrauterine insemination and childhood epilepsy was attenuated when a diagnosis of epilepsy plus two prescriptions for antiepileptic drugs were required. The results of the remaining sensitivity analyses were similar to those reported.

Discussion

In this large cohort study, we found that children conceived after ovulation induction or intrauterine insemination were at slightly increased risk of childhood epilepsy and that the risk was related to the use of clomiphene citrate. For IVF or intracytoplasmic sperm injection, our analyses suggested a small increased risk of idiopathic generalized epilepsy, a subtype of epilepsy believed to be of polygenic origin²⁵.

The present study has several methodologic strengths. The large sample size and the possibility to perform sibling analyses allowed us to assess differences in risk of developing epilepsy for exposed and unexposed sib pairs, which keeps maternal genetic and other family specific non-time varying influences constant. Sibling designs are particularly suitable for studying prenatal exposures and childhood outcomes as in the present study²⁶. However, parental infertility can be caused by both stable factors, e.g. genetics, and factors that may change between pregnancies, such as lifestyle factors or parental age. However, we aimed to diminish these potential biases by adjusting the sibling analyses for maternal age and smoking as well as the child's year of birth. Unfortunately, we could not assess the association between IVF or intracytoplasmic sperm injection and idiopathic generalized epilepsy in a sibling analysis approach because of the limited number of children born after either treatment who developed this subtype of epilepsy.

Another strength of the present study was the use of nationwide health registers to obtain detailed and valid information about exposures and outcomes. The coverage of the Danish IVF register is believed to be close to 100%¹². Information on hormonal treatment from redeemed prescriptions may lead to exposure misclassification if compliance with the

prescribed medication is low. However, women seeking fertility treatment are highly motivated to adhere to the treatment, and thus high compliance is expected. Furthermore, the hormones used to identify children born after ovulation induction or intrauterine insemination are only prescribed for fertility treatment. Children developing epilepsy were identified from two different data sources to ensure completeness of case identification. Epilepsy diagnoses in the Danish National Patient Register have previously been validated among adults with a reported positive predictive value of 81%²⁷. Additionally, the redemption of at least two prescriptions for antiepileptic drugs was required to ensure that the child had epilepsy. However, the subtype classification of childhood epilepsy in the Danish National Patient Register may be less precise and subject to non-differential misclassification, which may have attenuated the reported associations. If parents who conceive after fertility treatment are more prone to seek health care than parents who conceive spontaneously, exposed children could be diagnosed more frequently⁹ or earlier in the course of disease. This could lead to differential misclassification of the outcome and overestimation of the association. Although this may be true for some disorders, it is less likely to have biased our results, since epileptic seizures in children prompt immediate health care contact, in most circumstances.

Loss to follow-up after birth is unlikely to have influenced our results, since only few children were censored due to emigration or death during the follow-up period. Furthermore, we applied multiple imputation to avoid selection due to missing data. However, restricting our study population to live-born children may have attenuated the associations even though this potential bias would have been minimized by accounting for some of the common causes of prenatal death and childhood epilepsy²⁸.

The associations reported in the present study may reflect treatment effects or possibly residual confounding by parental characteristics that cause both infertility and childhood epilepsy. This source of potential confounding was addressed in the sibling design of clomiphene citrate exposure. The risk of epilepsy was substantial in the sibling analysis further corroborating that exposure to clomiphene citrate may be responsible for the increased risk of child epilepsy. Periconceptional treatment with clomiphene citrate has been associated with offspring neural tube defects in a previous animal study²⁹, although this finding remains controversial in human studies^{30,31}. Our study supports the hypothesis that clomiphene citrate may have an impact on the developing central nervous system. However, the biologic mechanism by which clomiphene citrate administration prior to ovulation may induce epilepsy in the offspring remains unknown. Young et al. (1999) showed that clomiphene citrate accumulates in the body over consecutive cycles³², and hormone sensitivity may start during early embryonic stages (the first weeks after fertilization)³³. One may speculate that clomiphene citrate affects the epigenetic regulation at this early stage of brain development³⁴, resulting in a lower threshold for seizures in the child. Since the association between IVF or intracytoplasmic sperm injection and idiopathic generalized epilepsy in the offspring could not be assessed in a sibling analysis, we cannot rule out the possibility of confounding due to uncontrolled non-time varying parental characteristics. Furthermore, the association was limited to a subtype of epilepsy believed to be of genetic origin, suggesting that the association may be attributable to parental genetics causing both infertility and epilepsy in the child.

An association between fertility treatment and childhood epilepsy has previously been shown in a study of some 80,000 singletons from the Danish National Birth Cohort (1997 to 2003) followed to a median age of 3.3 years. Results related to ovulation induction or intrauterine insemination were similar to those related to IVF or intracytoplasmic sperm injection with an increased incidence rate of childhood epilepsy of around 80%. Additionally, the study showed an increased risk in infertile couples receiving no fertility treatment (incidence rate ratio 1.38)⁸. However, the information on fertility and fertility treatment was self-reported, and potential underreporting of less invasive types of fertility treatment may explain the association with infertility, i.e. if ovulation induction- or intrauterine insemination-treated women are misclassified into the infertile, untreated group. Similarly, in a study of 16,120 children conceived by IVF with a median follow-up time of 5.5 years, Kallén et al. (2005) reported an association between IVF or intracytoplasmic sperm injection and childhood epilepsy in the crude analyses. However, this association disappeared after adjustment for potential confounders, including years of unwanted childlessness (adjusted odds ratio 1.14; 95% CI: 0.77 – 1.70)⁹. These previous studies identified children with epilepsy by hospital diagnoses only^{8,9}, whereas we were also able to use prescriptions for antiepileptic drugs. Unfortunately, duration of infertility is not recorded in any of the Danish national health registers, and thus we were unable to include this information in our analyses. Klemetti et al. (2006 and 2010) reported a tendency towards a small increased risk of childhood epilepsy in 2,911 children conceived after IVF and 3,912 children conceived after ovulation induction or intrauterine insemination compared with spontaneously conceived children. However, these children were only followed until the age of two years^{35,36}. Additionally, a cohort study aiming to identify risk factors of childhood epilepsy showed an association with assisted reproductive technology³⁷. However, these studies did not account sufficiently for potential confounders, including parental infertility.

Conclusion

The results of our study suggest that children conceived by ovulation induction or intrauterine insemination with clomiphene citrate may have a small increased risk of childhood epilepsy. Additional studies targeting this treatment are needed, since alternative hormonal treatment for ovulation induction and intrauterine insemination is available³⁸. Furthermore, children conceived by IVF or intracytoplasmic sperm injection may be at slightly increased risk of idiopathic generalized epilepsy. However, this association may be due to characteristics of the parents related to both parental infertility and epilepsy in the offspring rather than the treatments per se. Future studies are needed that assess the risk of idiopathic generalized epilepsy after IVF or intracytoplasmic sperm injection.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1
Maternal and infant characteristics according to types of fertility treatment in 565,116 singleton pregnancies, Denmark, 1995–2003

Characteristic	No fertility treatment n = 541,641	OI or IUI n = 14,985	IVF or ICSI n = 8,490	Total n = 565,116
Maternal characteristics				
Age, mean years (SD)	30 (4.6)	32 (4.4)	34 (3.9)	30 (4.6)
Primiparous, n (%)	223,256 (41)	9,132 (61)	6,206 (73)	238,594 (42)
Smoking during pregnancy, n (%)	120,353 (22)	2,331 (16)	1,497 (18)	124,181 (22)
Educational level				
Primary school, n (%)	108,519 (20)	2,059 (14)	1,183 (14)	111,761 (20)
Secondary school, n (%)	54,925 (10)	1,266 (8.5)	552 (6.5)	56,743 (10)
Higher education (2 to 3 years), n (%)	188,309 (35)	5,532 (37)	2,996 (35)	196,837 (35)
Higher education (>3 to 5 years), n (%)	80,116 (15)	2,501 (17)	1,441 (17)	84,058 (15)
Higher education (5 years), n (%)	38,623 (7.1)	1,337 (8.9)	735 (8.7)	40,695 (7.2)
Non-Western origin, n (%)	37,521 (6.9)	678 (4.5)	308 (3.6)	38,507 (6.8)
Maternal epilepsy diagnosis, n (%)	4,472 (0.8)	143 (1.0)	61 (0.7)	4,676 (0.8)
Infant characteristics				
Male gender, n (%)	277,980 (51)	7,744 (52)	4,481 (53)	290,205 (51)
Calendar year at birth				
1995–1997, n (%)	187,884 (35)	3,608 (24)	2,012 (24)	193,504 (34)
1998–2000, n (%)	180,471 (33)	5,372 (36)	2,737 (32)	188,580 (33)
2001–2003, n (%)	173,286 (32)	6,005 (40)	3,741 (44)	183,032 (32)
Preterm birth (<37 weeks), n (%)	24,837 (4.6)	979 (6.5)	789 (9.3)	26,605 (4.7)
Birth weight, mean grams (SD)	3,539 (570)	3,485 (628)	3,389 (646)	3,536 (573)
Cesarean section, n (%)	76,440 (14)	3,317 (22)	2,220 (26)	81,977 (15)
Apgar score (5 minutes) <7, n (%)	4,751 (0.9)	176 (1.2)	100 (1.2)	5,027 (0.9)
Follow-up time, median years (interquartile range)	14.3 (11.9 – 16.7)	13.5 (11.5 – 15.8)	13.2 (11.2 – 15.6)	14.3 (11.8 – 16.6)

ICSI: Intracytoplasmic sperm injection, IUI: Intrauterine insemination, IVF: In vitro fertilization, OI: Ovulation induction, SD: Standard deviation

TABLE 2

Associations between types of fertility treatment and the development of childhood epilepsy in 565,116 singleton pregnancies, Denmark, 1995–2003

Exposure	Pregnancies, n (%)	Epilepsy, n (%)	Person-years at risk	HR	HR (95% CI) adjusted ^a
No fertility treatment	541,641 (96)	7,726 (1.4)	7,531,427	1.00 (reference)	1.00 (reference)
OI or IUI	14,985 (2.7)	225 (1.5)	200,593	1.10	1.15 (1.00 – 1.31)
IVF or ICSI	8,490 (1.5)	120 (1.4)	112,099	1.05	1.10 (0.91 – 1.32)

^a Adjusted for maternal age at birth, maternal smoking during pregnancy, maternal educational level, maternal ethnicity, maternal diagnosis of epilepsy prior to birth, and child's year of birth
CI: Confidence interval, HR: Hazard rate ratio, ICSI: Intracytoplasmic sperm injection, IUI: Intrauterine insemination, IVF: In vitro fertilization, OI: Ovulation induction

TABLE 3

Associations between types of fertility treatment and the development of idiopathic generalized epilepsy or focal epilepsy in 565,116 singleton pregnancies, Denmark, 1995–2003

Exposure	Idiopathic generalized epilepsy		Focal epilepsy	
	n (%)	HR (95% CI) adjusted ^a	n (%)	HR (95% CI) adjusted ^a
No fertility treatment	1,492 (0.3)	1.00 (reference)	1,651 (0.3)	1.00 (reference)
OI or IUI	52 (0.4)	1.36 (1.03 – 1.79)	56 (0.4)	1.27 (0.97 – 1.66)
IVF or ICSI	30 (0.4)	1.43 (0.99 – 2.05)	25 (0.3)	1.01 (0.68 – 1.50)

^a Adjusted for maternal age at birth, maternal smoking during pregnancy, maternal educational level, maternal ethnicity, maternal diagnosis of epilepsy prior to birth, and child's year of birth

CI: Confidence interval, HR: Hazard rate ratio, ICSI: Intracytoplasmic sperm injection, IUI: In vitro fertilization, OI: Ovulation induction

Associations between fertility treatment and the development of childhood epilepsy stratified by treatment type and indication in 565,116 singleton pregnancies, Denmark, 1995–2003

TABLE 4

Exposure	Pregnancies, n	HR	HR (95% CI) adjusted ^a
No fertility treatment	541,641	1.00 (reference)	1.00 (reference)
OI or IUI			
Clomiphene citrate ^b	4,877	1.35	1.38 (1.12 – 1.69)
Follicle-stimulating hormone ^b	368	0.63	0.66 (0.21 – 2.04)
Human chorionic gonadotropin ^b	771	0.73	0.75 (0.38 – 1.51)
IVF or ICSI			
Procedure			
IVF	5,195	1.09	1.13 (0.90 – 1.41)
ICSI	2,389	1.01	1.09 (0.76 – 1.54)
Type of gamete ^c			
Fresh embryo	7,775	1.04	1.09 (0.90 – 1.31)
Frozen embryo	715	1.12	1.18 (0.65 – 2.12)
Donor semen	291	0.95	0.98 (0.37 – 2.62)
Indication ^c			
Male factor	2,819	1.03	1.09 (0.79 – 1.50)
Ovulation factor	925	1.17	1.26 (0.75 – 2.14)
Tubal factor	3,144	1.21	1.23 (0.94 – 1.60)
Other	2,360	0.89	0.95 (0.65 – 1.37)

^a Adjusted for maternal age at birth, maternal smoking during pregnancy, maternal educational level, maternal ethnicity, maternal diagnosis of epilepsy prior to birth, and child's year of birth

^b As monotherapy

^c Exposure groups are not mutually exclusive

CI: Confidence interval, HR: Hazard rate ratio, ICSI: Intracytoplasmic sperm injection, IUI: Intrauterine insemination, IVF: In vitro fertilization, OI: Ovulation induction