Fertility treatment and childhood type 1 diabetes mellitus: a nationwide cohort study of 565,116 live births

Laura Ozer Kettner, M.D.,[a] Niels Bjerregaard Matthiesen, Ph.D.,[a] Cecilia Høst Ramlau-Hansen, Ph.D.,[b] Ulrik Schiøler Kesmodel, Ph.D.,[c] Bjørn Bay, Ph.D.,[d] and Tine Brink Henriksen, Ph.D.[a]

[a] Perinatal Epidemiology Research Unit and Department of Pediatrics, Aarhus University Hospital, Aarhus; [b] Department of Public Health, Section for Epidemiology, Aarhus University, Aarhus; [c] Fertility Clinic, Department of Obstetrics and Gynecology, Herlev University Hospital, Herlev; and [d] Fertility Clinic, Department of Obstetrics and Gynecology, Aarhus University, Regional Hospital Horsens, Horsens, Denmark

Objective: To investigate the association between specific types of fertility treatment and childhood type 1 diabetes mellitus.
Design: Nationwide birth cohort study.
Setting: Not applicable.
Patient(s): All pregnancies resulting in a live-born singleton child in Denmark from 1995 to 2003.
Intervention(s): Not applicable.
Main Outcome Measure(s): Childhood type 1 diabetes mellitus identified from redeemed prescriptions for insulin until 2013.
Result(s): The study included 565,116 singleton pregnancies. A total of 14,985 children were conceived by ovulation induction or intrauterine insemination, and 8,490 children were conceived by in vitro fertilization or intracytoplasmic sperm injection. During the follow-up period, 2,011 (0.4%) children developed type 1 diabetes mellitus. The primary analyses showed no association between fertility treatment and childhood type 1 diabetes mellitus. In secondary analyses, ovulation induction or intrauterine insemination with follicle-stimulating hormone was associated with an increased risk of type 1 diabetes mellitus (hazard ratio 3.22; 95% confidence interval 1.20 to 8.64). No clear associations were seen with other types of fertility treatment or with specific treatment indications.
Conclusion(s): No association between fertility treatment and childhood type 1 diabetes mellitus was found. Ovulation induction or intrauterine insemination with follicle-stimulating hormone may be associated with an increased risk of childhood type 1 diabetes mellitus. However, this finding may be due to chance or to confounding by indication and thus requires further investigation. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)
Key Words: Assisted reproductive technology, in vitro fertilization, intracytoplasmic sperm injection, intrauterine insemination, ovulation induction, type 1 diabetes mellitus

Discuss: You can discuss this article with its authors and with other ASRM members at https://www.fertstertdialog.com/users/16110-fertility-and-sterility/posts/11825-fertility-treatment-and-childhood-type-1-diabetes-mellitus-a-nationwide-cohort-study-of-565-116-live-births

Infertility, defined as the inability to achieve a pregnancy within 1 year of trying to become pregnant (1), is experienced by one in six couples during their reproductive lifetime (2). Consequently, a large number of children are conceived after fertility treatment. According to the latest world report, more than 5 million children have been born after in vitro fertilization (IVF) since the introduction of the treatment in 1978 (2). Additionally, a large number of children have been born after less invasive types of fertility treatment, including ovulation induction (OI) and intrauterine insemination (IUI) (3). Fertility treatment implies external influences on the gametes and the embryo, which has raised concerns as to whether the treatments may have an impact on the health of the developing child. It is well established that fertility treatment is associated with an increased risk of adverse pregnancy outcomes, even in singleton births (4). However, exposure during

Received May 25, 2016; revised August 15, 2016; accepted September 7, 2016.
L.O.K. has nothing to disclose. N.B.M. has nothing to disclose. C.H.R.-H. has nothing to disclose. U.S.K. performed teaching sessions for Merck Serono and Ferring. B.B. has nothing to disclose. T.B.H. has nothing to disclose.
Supported by Aarhus University, the Aase and Ejnar Danielsen Foundation, the A.P. Møller Foundation for the Advancement of Medical Science, the Danish Doctors' Insurance Association Sponsored by SEB Pension, the Niels Bohr Foundation, the Torben and Alice Frimodt Foundation, Carl and Ellen Hertz's Grant, Managing Director Jacob Madsen and Olga Madsen's Foundation, the Foundation of 1870, the Oticon Foundation, the Lundbeck Foundation, and Professor Torben Iversen's Travel Grant. The study funders/sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.
Reprint requests: Laura Ozer Kettner, M.D., Perinatal Epidemiology Research Unit and Department of Pediatrics, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, 8200 Aarhus N, Denmark (E-mail: laura@kettner.nu).

Fertility and Sterility® Vol. ■, No. ■, ■ 2016 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2016.09.009

crucial developmental stages may also have an impact on a child's health later in life (5). Existing studies have suggested an increased risk of specific diseases in childhood such as asthma, epilepsy, and genitourinary diseases (6). Yet long-term follow-up studies of children conceived after fertility treatment remain sparse.

Childhood type 1 diabetes mellitus is a chronic disease caused by an autoimmune response leading to the destruction of the insulin-producing islet cells in the pancreas (7). Although the incidence of the disease is increasing, especially in children younger than 5 years old (8), the etiology behind the disease remains unclear. Genetic susceptibility as well as environmental triggers are suspected (9), and the increase in the incidence has largely been attributed to environmental exposures (8). It has been suggested that early life exposures may affect the development of the immune system and thus increase the risk of immune dysfunction or immune diseases later in life (10) such as type 1 diabetes mellitus. One previous study indicated an association between IVF and childhood type 1 diabetes mellitus (11). However, the study was small, and the duration of follow-up observation was very short. We investigated the association between the use of specific types of fertility treatment and the development of childhood type 1 diabetes mellitus in a large, nationwide birth cohort with long-term follow-up records.

MATERIALS AND METHODS

Design and Population

Our nationwide birth cohort study included all pregnancies resulting in a live-born singleton child in Denmark from January 1, 1995 until December 31, 2003. We identified the study population from the Danish Medical Birth Registry in which all children born in Denmark have been recorded since 1973 (12). By use of the unique personal identification number allocated to all legal Danish residents, we obtained individual-level information on all study participants from the Danish IVF register (13), the Danish National Prescription Registry (14), and Statistics Denmark (15-17). Spontaneous pregnancies in women younger than 20 years were excluded from the cohort because all women conceiving after fertility treatment were at least 20 years old.

Fertility Treatment

The Danish IVF register was used to identify children conceived after IVF or intracytoplasmic sperm injection (ICSI). Since 1994, each initiated IVF cycle at both public and private fertility clinics in Denmark has been reported to this register along with information on treatment indication, hormone treatment, the specific procedure, and the outcome of the treatment (13).

Fertility treatment with OI or IUI was identified from redeemed hormone prescriptions recorded in the Danish National Prescription Registry. Since 1995, all prescription drugs sold at Danish pharmacies have been recorded in this register according to the Anatomical Therapeutic Codes (ATC) of the drugs along with the exact dispensing date (14). Inclusion in the OI or IUI group required [1] the redemption of a maternal prescription consistent with OI or IUI treatment before the index pregnancy and [2] no record in the Danish IVF register during the relevant time period, as the same hormones may also be used for IVF or ICSI treatment. Hormones used to identify women treated with OI or IUI included clomiphene citrate, follicle-stimulating hormone (FSH), and human chorionic gonadotropin. The hormones had to be redeemed within the time period from 12 weeks before to 4 weeks after the last menstrual period recorded in the Danish Medical Birth Registry. This time period was chosen because hormone treatment for OI or IUI can be prescribed for up to 12 weeks at a time.

Diabetes Mellitus Type 1

Children were categorized as having diabetes mellitus type 1 if they were registered with at least one redeemed prescription for insulin (ATC A10A) (18) in the Danish National Prescription Registry. This approach was chosen over the use of diagnoses from the Danish National Patient Register (19) because hospital diagnoses may be subject to misclassification, whereas the redemption of a prescription for insulin is considered an exact indicator of the development of childhood type 1 diabetes mellitus.

Covariates

The following maternal and infant characteristics were obtained from the Danish Medical Birth Registry: maternal age, parity, smoking during pregnancy, ethnicity, child's year of birth, gender, gestational age, birth weight, Apgar score, and whether the child was delivered by cesarean delivery. Information on parental history of type 1 diabetes mellitus before birth was obtained from redeemed prescriptions for insulin recorded in the Danish National Prescription Registry. Information on maternal education as well as the child's vital status and emigration history during the follow-up period was obtained from Statistics Denmark.

Statistical Analyses

All analyses were performed in Stata 14 (StataCorp). The risk of type 1 diabetes mellitus was estimated using Cox proportional hazards regression. We included each child's time at risk computed from the date of birth until whichever event came first: redemption of the first prescription for insulin, death, emigration, or end of the follow-up period on December 31, 2013. We estimated hazard rate ratios and 95% confidence intervals. Log-log plots as well as predicted survival plots were used to verify the assumption of proportional hazards, and robust standard errors were used to account for correlations between siblings in the cohort.

In the primary analyses, children conceived by [1] IVF or ICSI or [2] OI or IUI were compared with a control group of spontaneously conceived children regarding the development of type 1 diabetes mellitus in childhood. In secondary analyses, the risk associated with maternal exposure to OI or IUI treatment was estimated according to the specific type of hormone used as monotherapy (clomiphene citrate, FSH, human chorionic gonadotropin). Furthermore, the risk associated with IVF