Reproductive function in the sons of women who experienced stress due to bereavement before and during pregnancy: a nationwide population-based cohort study

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Objective: To estimate the association between prenatal exposure to maternal stress and reproductive disorders in Danish men, where prenatal stress exposure was defined as the mother's loss of a close relative during pregnancy or in the 12 months before conception.
Design: Population-based cohort study.
Setting: Not applicable.
Patient(s): All males born in Denmark between 1973 and 2008 (n = 1,217,576) and observed for up to 39 years.
Intervention(s): None.
Main Outcome Measure(s): Male reproductive function, defined using a composite outcome including congenital malformations of genital organs, testicular cancer, diagnosis of male infertility, or assisted conception use due to male factor infertility.
Result(s): In total, 28,986 men (2.4%) had been exposed to prenatal stress, and 62,929 (5.2%) experienced the composite outcome during the follow-up period. Prenatal exposure to stress was associated with an elevated risk of reproductive problems (hazard ratio [HR] 1.09; 95% CI, 1.04–1.15). The association was stronger when the exposure occurred during the first trimester of pregnancy, and for congenital malformations of genital organs. When focusing on infertility alone, we saw no evidence of increased risk (HR 0.90; 95% CI, 0.77–1.06). In addition, the probability of marrying a woman was lower for exposed men (HR 0.93; 95% CI, 0.89–0.98).
Conclusion(s): Prenatal stress in the form of the mother's bereavement during the first trimester of pregnancy is associated with a higher risk of reproductive disorders from congenital malformations of the genital organs in the male offspring. The lack of an association between maternal bereavement and later infertility in the exposed male offspring may be due in part to the men's lower probability of attempting to have children. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)
Key Words: Bereavement, cryptorchidism, hypospadias, pregnancy, stress, male infertility, reproductive function

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Denmark is among the countries with the highest use of medically assisted reproduction (1). Among children born in 2014, 8% were conceived using these techniques, half of them with in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) (2). Use of ICSI is often associated with poor sperm quality. It is estimated that a male factor, alone or in combination with a female factor, is present in 40% to 50% of couples who experience infertility (3).

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The etiology of male infertility remains largely unknown; certain congenital anomalies such as cryptorchidism and hypospadias, and some adult conditions such as poor sperm quality and testicular cancer, are considered symptoms of disrupted developmental of the reproductive system (4). Several prenatal exposures, mostly environmental, have been hypothesized to play a role in this syndrome (4, 5), but limited evidence exists for a role of maternal stress. In animal studies, maternal stress during pregnancy has been shown to affect fertility and reproductive behavior in the offspring (6–10). In humans, previous studies have suggested that men and women prenatally exposed to maternal bereavement had their first child slightly later and ended up with slightly fewer children (11, 12). Additionally, women born to mothers who had experienced bereavement during the first trimester of pregnancy were more likely than unexposed women to be diagnosed with infertility or to receive treatment (13).

In this study, we use several Danish population-based registries to examine the association between exposure to maternal bereavement after the death of a close relative before or during pregnancy and subsequent risk of reproductive disorders in sons, using a composite outcome of congenital malformations of genital organs, testicular cancer, and infertility.

MATERIALS AND METHODS

Our population-based cohort included 1,229,375 males born in Denmark between 1973 and 2008. Information was obtained from several Danish national registers, linked through the unique personal identification number assigned to all live-born children (Supplemental Table 1, available online). The Danish Civil Registration System (CRS) (14) contains information on all persons living in Denmark, including sex, date and place of birth, migration status, and identity of the parents, with continuously updated information on vital status, place of residence, and spouses, among other factors. This register permits the identification of all individuals and the linkage to their family members. To increase the likelihood of identifying close relatives of the mother in the registers, we restricted the study to men born to mothers of Danish origin. We excluded 11,799 men (1.0%) whose mothers could not be linked to any living relative during the relevant time period. The final study population consisted of 1,217,576 men born to 862,265 mothers (Supplemental Fig. 1, available online).

Exposure Definition

Men were considered exposed if their mother had lost an older child (including stillbirths), a parent, or a sibling during pregnancy or in the 12 months preceding conception. The exposure also included the death of a spouse/partner (the registered father of the index man) from the time of estimated conception through the end of pregnancy. The conception date was estimated by subtracting gestational age (GA) at birth (in days) from the date of birth. The GA was obtained from the Medical Birth Registry (MBR) (15) and was predominantly based on the date of the last menstrual period in the early years and on ultrasound in the later years. The GA was missing for all 180,090 boys born between 1973 and 1977, and in 89,100 (8.6%) of those born from 1978 and onward. For these individuals, the GA was assumed to be 39, 35, 32, and 31 weeks for singletons, twins, triplets, and quadruplets, respectively. These values were chosen as they have been used in previous studies (16); however, to assess whether this imputation had an impact on the estimates, we performed several sensitivity analyses, including only men with an observed GA and imputing different values for the missing GA, as previously described elsewhere (13).

Outcome Definition

We defined disorders of male reproductive function using a composite outcome, including congenital malformations of genital organs, testicular cancer, and diagnoses or treatment for male infertility. This information was obtained from two different registers: [1] the Danish National Hospital Register (NHR) (17), which includes all nonpsychiatric discharge diagnoses from hospitals since 1977 (from 1995, also outpatient diagnoses); and [2] the Danish In Vitro Fertilization Register (IVFR) (18), which was established in 1994 and covers all IVF/ICSI treatments with fresh and frozen embryos performed in public and private fertility clinics, regardless of whether they resulted in a pregnancy, but not ovulation induction or intrauterine insemination during the study period.

Diagnoses obtained from the NHR included male infertility, congenital malformations of genital organs (cryptorchidism, hypospadias, and other), and testicular cancer. Male infertility was also identified by a link to a female partner with a diagnosis of "female infertility associated with male factors." A woman was considered as the man's partner if she was married to him at the time of diagnosis or if she cohabited with him without being his mother, daughter, or sister. (In a sensitivity analysis, a man and a woman living together were not considered partners if there were other people living in the same address who were not close relatives.) We treated these relationships as time-varying in the analysis, starting on the day couples were married or moved in together and ending on the day they were divorced or moved apart (based on information obtained from the CRS).

In the IVFR, each treatment is identified by the woman's identification number, while the male's identification number is not always available. We considered a man to have an infertility diagnosis when a treatment cycle was performed because of male factor infertility, provided that the man had not had a previous vasectomy. When the man's identification number was missing, a man was considered as having an infertility problem if he was married or cohabitated with the identified woman at the time of treatment, based on the above definition.

Outcome "occurrence" was approximated by the date of any of the above diagnoses or treatments. We used the same approach for congenital malformations, even though they would have been present at birth. We performed a subanalysis starting the follow-up period at 18 years and focusing on infertility (thus ignoring malformations of genital organs and testicular cancer). This subanalysis was