ORIGINAL ARTICLE: ENVIRONMENT AND EPIDEMIOLOGY

Maternal endometriosis and genital malformations in boys: a Danish register-based study

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Objective: To investigate the association between maternal endometriosis and occurrence of the genital anomalies cryptorchidism and hypospadias in sons.
Design: Population-based cohort study.
Setting: Not applicable.
Patient(s): All live-born singleton boys born from 1978 to 2012.
Intervention(s): None.
Main Outcome Measure(s): Cryptorchidism and hypospadias in boys based on information from the Danish National Patient Register.
Result(s): The study included 1,073,026 live-born singleton boys. A total of 6,443 boys were sons of women diagnosed with endometriosis before pregnancy. Altogether, 27,342 boys were diagnosed with cryptorchidism, of whom 16,446 had corrective surgery. Hypospadias was diagnosed in 4,853 boys. As compared with unexposed boys, a tendency towards a slightly higher occurrence of cryptorchidism was observed among boys of women with endometriosis (adjusted hazard ratio [aHR] 1.18; 95% confidence interval [CI], 0.97, 1.44). When stratified by medically assisted reproduction (MAR) technologies, the association was slightly stronger among boys born to women with endometriosis who had conceived via MAR, yet it remained moderate and statistically insignificant (aHR 1.27; 95% CI, 0.97, 1.70). When women who conceived with MAR were excluded, the association between endometriosis and cryptorchidism disappeared. For hypospadias, we observed no association, either in the main analysis or the stratified analysis.
Conclusion(s): The findings from this register-based study do not provide strong evidence for a higher occurrence of the studied genital anomalies among boys of women with endometriosis. (Fertil Steril® 2017;■:■–■. ©2017 by American Society for Reproductive Medicine.)
Key Words: Chronic diseases, cryptorchidism, infertility, hypospadias, pregnancy

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Endometriosis is an estrogen-dependent chronic disease, defined by ectopic occurrence of endometrium-like tissue abnormally implanted in various locations outside the uterine cavity with subsequent local inflammation (1). The main symptoms are infertility, fatigue, and pelvic pain, often with disabling effects (2). Endometriosis may occur at any age, from premenarche until after menopause, but the symptoms and diagnosis are most common among women of reproductive age. It remains unclear how common endometriosis is; the prevalence estimates range from 2% to 10% in the general female population and are higher among infertile women (3, 4). Despite the high prevalence of endometriosis and the associated morbidity and concomitant health care costs (5), the etiology and pathogenesis of endometriosis remain poorly understood.

Although the disease prevalence peaks during reproductive age and endometriosis complicates both conception and pregnancy, the health of children

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born to women with endometriosis has not received much attention until recently. Newly published studies have found that women with endometriosis are more likely to experience pregnancy complications, including miscarriage and ectopic pregnancy (6). Further, the literature indicates that women with endometriosis have a higher risk of preterm birth (7–11), although conflicting results exist (12–14).

Whether endometriosis gives rise to a higher occurrence of congenital abnormalities remains unknown. A case-control study by Mavrogenis et al. (15) investigated possible associations of various maternal factors and the genital anomaly cryptorchidism (undescended testis). In a small study, the investigators showed twice the risk of cryptorchidism among sons born to mothers with endometriosis (15). Generally, nongenetic maternal factors seem important in the etiology of cryptorchidism (16). This is, however, the only previous study on the subject and given the widespread occurrence of endometriosis, a deeper understanding of both short- and long-term consequences for the children born to women with the disease is needed. Our large, population-based study investigated whether endometriosis is associated with the genital anomalies cryptorchidism and hypospadias.

MATERIALS AND METHODS

Study Population

In a population-based cohort study in Denmark, we included all live-born singleton boys born from January 1, 1978, to December 31, 2012, recorded in the Danish Medical Birth Register (17). Using the person-unique national registration number assigned to all Danish residents (18), the Medical Birth Register was cross-linked with other nationwide registers: the Danish National Patient Register (19), the Danish Integrated Database for Labour Market Research (20), and the In Vitro Fertilization (IVF) register (21). The Danish Medical Birth Register was established in 1973 and collects data on more than 99% of all births each year in Denmark (17). It is based on mandatory reporting by the attending midwife or physician, shortly after both in-hospital and in-home deliveries.

Exposure Classification

From the Danish National Patient Register (19), information on hospital discharge diagnoses of endometriosis from inpatient and outpatient hospital visits were available. For the period covered by the study, the International Classification of Disease 8 (ICD-8) was used in Denmark from 1978 to 1993, and the ICD-10 was used from 1994 to 2012 (Table 1). We classified women as having endometriosis if they were registered with a hospital discharge diagnosis code of endometriosis before conception: ICD-8: 6253*; or ICD-10: N80*. In the main analysis, all subtypes of endometriosis were included and studied as one disease entity.

Due to no or nonspecific symptoms and lack of awareness in the health care system, endometriosis may have an extended diagnostic delay (22, 23). The disease thus may have affected women long before the diagnosis was registered, and women diagnosed after pregnancy may have had the disease before and during pregnancy. Therefore, we also assessed the risk of genital anomalies among women diagnosed with endometriosis at any time up until end of the follow-up period (December 31, 2012). As we hypothesized that women whose disease was diagnosed before pregnancy may have experienced more severe disease during the fertilization, implantation, and the in utero periods, we assessed endometriosis diagnosed before and after pregnancy seperately. Thus, we categorized the exposure as no diagnosis of endometriosis, endometriosis diagnosed at any time up until end of follow-up, endometriosis diagnosed before conception of the index child, and endometriosis diagnosed after conception of the index child or in later life up until end of the follow-up period.

Outcome Classification

Information about cryptorchidism, hypospadias, and corrective surgery were obtained from the Danish National Patient Register (19). Cryptorchidism was defined as boys with a main diagnosis of cryptorchidism (ICD-8: 75210, 75211,

TABLE 1

Number of diagnoses with endometriosis subtypes according to the International Classification of Diseases, the 8th and 10th versions (ICD-8 and ICD-10).

			Time of diagnosis, n (%)[a]	
Maternal endometriosis definition	**ICD-10 (1994–2012)**	**ICD-8 (1978–1993)**	**Before conception**	**After conception**
Any endometriosis diagnosis	N80[b]	6253[b]	6,443 (0.60)	13,793 (1.29)
Uterus (adenomyosis)	N800	62531	462 (0.04)	3,920 (0.37)
Ovary	N801	62530	2,205 (0.21)	3,903 (0.36)
Fallopian tube	N802	62532	307 (0.03)	363 (0.03)
Pelvic peritoneum	N803	62533	2,190 (0.20)	2,482 (0.23)
Rectovaginal septum or vagina	N804	62535	361 (0.03)	586 (0.05)
Intestine	N805	62536	78 (0.01)	187 (0.02)
Cutaneous scars	N806	62537	76 (0.01)	501 (0.05)
Other	N808	62534, 62538	907 (0.08)	2,004 (0.19)
Unspecified	N809	62539	2,477 (0.23)	5,445 (0.51)

[a] Distribution (numbers and percentages) of sons of mothers with each subtype of endometriosis among all 1,073,026 boys in the study population.
[b] All subcategories of N80 and 6253 included.

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