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.

Arendt. Endometriosis and male genital malformations. Fertil Steril 2017.

75219; and ICD-10: Q530, Q531, Q531A, Q532, Q532A, or Q539) that persisted until time of surgery (Surgery and Treatment Classification of the National Board of Health [STC]; 55600 and 55640 and Nordic Classification of Surgical Procedures [NCSP]: KFH00, KFH01, and KFH10). This approach has been previously shown to have the highest positive predictive value (24). Hypospadias was defined as boys registered with a main diagnosis of hypospadias (ICD-8: 75219, 75220, 75221, 75222, 75228, and 75229; and ICD-10: Q540, Q540A, Q541, Q542, Q543, Q548, and Q549.

Covariates

Selection of possible confounders was based on published literature and by use of directed acyclic graphs (25), and we included the following covariates in the analyses: maternal age at birth (<20, 20–29, 30–39, and ≥40 years), maternal years of education (≤9, 10–14, and ≥15 years), and maternal nationality (Nordic and non-Nordic countries). We further stratified the Cox regression model for calendar year at birth (<1985, 1985–1989, 1990–1994, 1995–1999, 2000–2005, >2005). Information on maternal cigarette smoking was available from the Danish Medical Birth Register from 1991 to 2012, and this information was used in a subanalysis where we adjusted for maternal cigarette smoking (smoker and nonsmoker).

Furthermore, from the IVF register (21), established in 1994, we had information on medically assisted reproduction (MAR) technologies, including conception through ovulation induction, ovarian stimulation, ovulation triggering, assisted reproductive technology procedures, and intrauterine, intracervical, and intravaginal insemination with semen of partner or donor (26). Because we consider MAR to be a potential intermediate factor, it was not adjusted for in the main model, but used in a secondary analysis.

Statistical Analyses

Missing information. In total, 97.6% had complete information on variables included in the main analyses. Although we had very few missing data, we addressed the missing information by use of a multiple imputation technique (27, 28). The method is explained in detail elsewhere, but in short it is shown to yield unbiased and more precise estimates than the complete case analysis when data are missing at random (29). We performed multiple imputation using chained equations and imputed 50 data sets. The following variables were included: diagnosis of endometriosis, diagnosis of cryptorchidism or hypospadias, diagnosis of other congenital abnormalities, calendar year at birth, maternal age at birth, parity, maternal years of education, maternal nationality, MAR birth weight, and gestational age at birth.

Data analyses. Follow-up started at birth, and the boys were followed in the registers until December 31, 2012. Thus, the follow-up time ranged from 0 to 35 years with a mean follow-up time of 17.1 years. Because the time of follow-up differed among participants and to take into account that the genital anomalies are diagnosed throughout infancy, we studied the association using Cox proportional hazards regression and calculated crude (cHR) and adjusted hazard ratios (aHR) with 95% confidence intervals (CI) for cryptorchidism and hypospadias. In the main analyses, we studied endometriosis as one disease entity. In secondary analyses, we further assessed the occurrence of cryptorchidism and hypospadias among sons of women with rectovaginal endometriosis, as this is a severe and infiltrative form of the disease (30). We also estimated the risk among sons of women with adenomyosis (endometriosis within the myometrium) because this condition specifically has been associated with a higher risk of preterm birth (31).

We followed the boys after birth until first diagnosis, emigration, death, or censoring at the end of the follow-up period (which ever came first). The data also included siblings and to account for dependence of sons born to the same mother, we applied robust standard errors. The proportional hazards assumption was visually inspected in log-minus-log plots and found satisfactory.

Subanalyses

Endometriosis is a risk factor for subfertility. Women with endometriosis are thus more likely to receive fertility treatment, which in itself has been suggested to increase the risk of congenital abnormalities. In a subanalysis we therefore studied the association between endometriosis diagnosed before birth and the genital anomalies stratified by use of MAR among singleton live-born boys born from 1994 to 2012.

Moreover, a number of further subanalyses were performed. [1] The diagnosis and registration of both exposure and outcome may have improved during the study period, so we restricted the study population to boys born in the ICD-10 period (1994 to 2012) and repeated the main analysis. [2] We repeated the analysis for cryptorchidism where we based the case ascertainment on all boys with the diagnosis, regardless of corrective surgery or not. [3] In the subpopulation of boys born from 1991 to 2012, we were able to also adjust for maternal cigarette smoking, which may act as a potential confounding factor. [4] As there may be systematic differences between nulliparous and multiparous women, we restricted the analyses to nulliparous women. [5] We repeated the analyses based on a multiple imputation model of 70 data sets instead of 50 data sets to assess the robustness of the main model. [6] Finally, we conducted a complete-case analysis. Data were analyzed in STATA 11.1 (Statacorp), on the secure platform of Statistics Denmark.

In Denmark, register-based studies do not require an institutional review board approval. We had no personal contact with the participants and followed all Danish rules and regulations for research. The study was approved by the Danish Data Protection Agency (reference 2013-41-1964).

RESULTS

The final study population comprised 1,073,026 mother-son pairs. There were 20,236 women registered with one or more diagnoses of endometriosis at any time from 1978 to 2012,

and among these 6,443 women received an endometriosis diagnosis before pregnancy and 13,793 after pregnancy of the index child (Table 1). The affected women often had more than one specific endometriosis diagnosis, and Table 1 presents the distribution of sons to mothers with each subtype of endometriosis. Further, of the 1,073,026 singleton live-born boys included, 4,853 boys (4.5 per 1,000) were diagnosed with hypospadias. In total, 27,342 boys (25.5 per 1,000) were diagnosed with cryptorchidism, of which 17,186 (16.0 per 1,000) underwent corrective surgery for cryptorchidism.

Table 2 shows the maternal characteristics according to maternal endometriosis exposure status. The frequency of endometriosis increased with the calendar year of birth. Compared to women without the disease, women with endometriosis were on average older at the time of birth, were more often nulliparous, had higher education level, and were more often of Nordic origin. Further, there was a markedly higher frequency of use of MAR among women with endometriosis (36.9%) compared with the women without endometriosis (5.6%).

In Table 3, the main results are presented. Our main exposure of interest was endometriosis diagnosed before pregnancy of the index child. Here, we observed a tendency toward a slightly higher occurrence of cryptorchidism among boys of mothers with endometriosis (aHR 1.18; 95% CI, 0.97, 1.44) compared with those unexposed. For hypospadias, we observed no association (aHR 1.02; 95% CI, 0.72, 1.44). When we assessed the association between endometriosis and genital anomalies among those mothers who were diagnosed after pregnancy, the associations for cryptorchidism were closer to the null.

In secondary analyses we assessed the occurrence of hypospadias and cryptorchidism among the sons of women with adenomyosis or rectovaginal endometriosis. We found no association between adenomyosis or rectovaginal endometriosis and cryptorchidism or hypospadias (results not shown), but the numbers were small (Table 1).

Of the 607,759 singleton live-born boys born during 1994 to 2012, 4,961 (0.8%) were sons of women with endometriosis diagnosed before pregnancy. Among them, 1,831 (36.9%) were registered with use of MAR in the index pregnancy. We performed analyses stratified by MAR and found a slightly stronger association between endometriosis and cryptorchidism among women who conceived with MAR, yet the association remained statistically insignificant (aHR 1.27; 95% CI, 0.97, 1.70) (Table 4). When women who conceived with MAR were excluded, the association between endometriosis and cryptorchidism disappeared. For hypospadias, no association was observed (see Table 4).

TABLE 2

Characteristics according to maternal endometriosis exposure status among 1,073,026 singleton boys, Denmark, 1978–2012.

		Time of endometriosis diagnosis	
Characteristic	**No endometriosis**	**Before birth**	**After birth**
Total, n (%)	1,052,790 (98.1)	6,443 (0.6)	13,793 (1.3)
Calendar year of birth, n (%)			
<1985	187,718 (17.8)	355 (5.5)	4,039 (29.3)
1985–1989	139,069 (13.2)	557 (8.6)	2,771 (20.1)
1990–1994	161,665 (15.4)	707 (11.0)	2,711 (19.6)
1995–1999	163,623 (15.5)	829 (12.9)	2,119 (15.4)
2000–2005	156,974 (14.9)	1,179 (18.3)	1,411 (10.2)
>2005	243,741 (23.2)	2,816 (43.7)	742 (5.4)
Maternal age (y) at birth, n (%)			
<20	26,374 (2.5)	17 (0.3)	552 (4.0)
20–29	584,422 (55.5)	2,181 (33.9)	9,244 (67.0)
30–39	423,448 (40.2)	4,016 (62.3)	3,909 (28.3)
≥40	18,546 (1.8)	229 (3.5)	88 (0.7)
Parity, n (%)			
1	469,400 (44.6)	3,076 (47.7)	6,590 (47.7)
≥1	578,431 (54.9)	3,317 (51.5)	7,181 (52.1)
Missing	4,959 (0.5)	50 (0.8)	22 (0.2)
Maternal years of education, n (%)			
Short (≤9 y)	212,448 (20.2)	1,019 (15.8)	3,665 (26.6)
Medium (10–14 y)	465,540 (44.2)	2,970 (46.1)	6,374 (46.2)
Long (≥15 y)	352,965 (33.5)	2,395 (37.2)	3,603 (26.1)
Missing	21,837 (2.1)	59 (0.9)	151 (1.1)
Maternal nationality, n (%)			
Nordic countries	997,692 (94.8)	6,273 (97.4)	13,417 (97.3)
Other countries	55,090 (5.2)	170 (2.6)	376 (2.7)
Missing	8 (<0.01)	0 (0.0)	0 (0.0)
MAR, n (%)[a]			
Yes	33,445 (5.6)	1,831 (36.9)	521 (10.9)
No	564,580 (94.4)	3,130 (63.1)	4,252 (89.1)

[a] Information on medical assisted reproduction (MAR) from the IVF-register among 607,759 singleton live-born boys born from 1994 to 2012.

Arendt. Endometriosis and male genital malformations. Fertil Steril 2017.

TABLE 3

Hazard ratios for cryptorchidism and hypospadias according to maternal endometriosis among 1,073,026 Danish singleton boys, Denmark, 1978–2012.

	Cryptorchidism				Hypospadias			
Endometriosis status	Total/cases (no.)	cHR	aHR[a]	95% CI	Total/cases (no.)	cHR	aHR[a]	95% CI
None	1,052,790/16,819	1.00	1.00	Ref	1,052,790/4,765	1.00	1.00	Ref
At any time	20,236/367	1.07	1.05	0.95; 1.17	20,236/88	0.94	0.99	0.80; 1.23
Before pregnancy	6,443/101	1.23	1.18	0.97; 1.44	6,443/32	1.20	1.02	0.72; 1.44
After pregnancy	13,793/266	1.02	1.01	0.90; 1.15	13,793/56	0.83	0.99	0.76; 1.29

Note: aHR = adjusted hazard ratio; cHR = crude hazard ratio; CI = confidence interval; Ref = reference.
[a] Adjusted for maternal age at birth in years (<20, 20–29, 30–39, and ≥40), maternal years of education (short ≤9 years, medium 10–14 years, and long ≥15 years), maternal nationality (Nordic countries and non-Nordic countries), and calendar year at birth (<1985, 1985–1989, 1990–1994, 1995–1999, 2000–2005, >2005).

Arendt. Endometriosis and male genital malformations. Fertil Steril 2017.

Subanalyses

With the data restricted to boys born during the ICD-10 period from 1994 to 2012, the results attenuated further toward the null (results not shown). When we included all boys diagnosed with cryptorchidism, the results were similar to those of the main analysis based on diagnosed cases verified by corrective surgery (results not shown). Among boys born from 1991 to 2012, we adjusted for maternal cigarette smoking and found the same association as in the main analysis (results not shown). Further, the association did not differ between nulliparous and multiparous women (results not shown). Finally, the results were robust to changes in the multiple imputation model, and they were similar to those from the complete-case analysis (results not shown).

DISCUSSION

This is the first population-based nationwide study exploring the association between endometriosis and the occurrence of genital anomalies in boys. Overall, we found a small tendency toward an association between endometriosis and cryptorchidism, especially among women who conceived with MAR. The results did not indicate that endometriosis leads to a higher risk of hypospadias.

To our knowledge, only one previous study has examined the association between maternal endometriosis and cryptorchidism in boys, and data on the potential association between maternal endometriosis and hypospadias has not previously been published. Our findings did not corroborate those of Mavrogenis et al. (15), although we did observe a tendency toward a slightly higher occurrence of cryptorchidism.

Mavrogenis et al. (15) performed a case-control study of 2,052 cases with isolated undescended testis and 24,814 controls, and they assessed several potential maternal risk factors, including endometriosis, in relation to the risk of cryptorchidism. Based on information from 39 exposed cases, they found a rather strong association with cryptorchidism (odds ratio 2.42; 95% CI, 1.71, 3.42). The discrepancy in our findings may be ascribed to disparities in selection to the two studies as well as ascertainment of endometriosis and cryptorchidism. In the study by Mavrogenis et al. (15), the 39 women had symptomatic endometriosis, and all received treatment for infertility whereas we used register-based data on all women with any diagnosis of endometriosis. Undoubtedly, in our study there is some underreporting of endometriosis, which is a limitation that could have attenuated the association toward the null. On the other hand, Mavrogenis et al. highlighted that the major limitation of their study was that their data were burdened by selection bias.

TABLE 4

Hazard ratios for cryptorchidism and hypospadias according to maternal endometriosis stratified by medically assisted reproduction (MAR) technologies, among 607,759 Danish singleton boys, Denmark, 1994–2012.

	Cryptorchidism				Hypospadias			
Endometriosis status	Total/cases (no.)	cHR	aHR[a]	95% CI	Total/cases (no.)	cHR	aHR[a]	95% CI
Women who conceived without MAR (n = 571,962)								
None	564,580/6,815	1.00	1.00	Ref	564,580/3,004	1.00	1.00	Ref
Before pregnancy	3,130/36	1.03	1.01	0.72; 1.40	3,130/18	1.11	1.11	0.70; 1.76
Women who conceived with use of MAR (n = 35,797)								
None	33,445/421	1.00	1.00	Ref	33,445/235	1.00	1.00	Ref
Before pregnancy	1,831/27	1.27	1.27	0.86; 1.88	1,831/11	0.87	0.88	0.48; 1.62

Note: aHR = adjusted hazard ratio; cHR = crude hazard ratio; CI = confidence interval; Ref = reference.
[a] Adjusted for maternal age at birth in years (<20, 20–29, 30–39, and ≥40), maternal years of education (short ≤9 years, medium 10–14 years, and long ≥15 years), maternal nationality (Nordic countries and non-Nordic countries), and calendar year at birth (1994–1999, 2000–2005, >2005).

Arendt. Endometriosis and male genital malformations. Fertil Steril 2017.

The major strength of our study was the population-based design with a large and unselected study population. The Danish health care registers are complete with regard to registrations of births, so our study is not strongly affected by selection bias. We had almost complete follow-up because losses from death and emigration were very low. It should, however, be noted that we considered miscarriages and stillbirths as losses to follow-up because they occurred after the onset of exposure. Theoretically, if women with endometriosis experienced fetal losses more often than other women, and further if the occurrence of genital anomalies was much higher among the lost fetuses than those surviving, it could have resulted in attenuated associations (32). We consider this scenario unlikely to have affected our results because cryptorchidism and hypospadias are not expected to increase the risk of fetal death much.

Another strength of our study was the ability to adjust for some important potential confounders and that we had information on MAR. Despite this, residual confounding or confounding from unmeasured factors cannot be ruled out. Because endometriosis is a strong risk factor for subfertility, use of MAR may mediate a possible causal link from endometriosis to the genital anomalies. We performed stratified analyses, but it is important to emphasize that stratification on MAR could open up for other confounding paths if there are unmeasured common causes of MAR and genital anomalies.

Information bias arises due to systematic incorrect information on exposure, outcome, or potential confounders; this is particularly important to consider in register-based studies. The diagnostic validity of the outcomes cryptorchidism and hypospadias in the Danish National Patient Register has been evaluated and is considered good (24, 33), although the milder cases may not be registered. We consider it a minor issue, but some random nondifferential misclassification of the genital anomalies may be present.

We also cannot rule out that the findings of no association are partly due to misclassified information on endometriosis. Ascertainment of endometriosis was based on diagnoses of endometriosis recorded at inpatient or outpatient visits at hospitals from the Danish National Patient Register, which generally has high quality and completeness (19). However, the study period spans several decades from 1978 to 2012 and during this time, the diagnostic criteria and registration of endometriosis have changed. One of the limitations of our study is that we had no information on histologic verification of endometriosis after surgery. The validity of the endometriosis diagnosis in the Danish National Patient Register remains unknown, but a few previous studies using register-based data for endometriosis ascertainment have supported this approach. A Swedish register-based study using information on endometriosis from the Swedish Patient Register found that the diagnosis was rather valid in that 81% of the diagnoses were histologically confirmed (34). Undoubtedly some misclassification is present, most likely nondifferential, as endometriosis was recorded before pregnancy, and therefore registration of endometriosis most likely did not depend on detection of the genital anomalies. Thus, this nondifferential misclassification could have attenuated the results toward the null.

In a subanalysis, we restricted our study population to the ICD-10 period. We reasoned that during this period both the sensitivity and the specificity of the diagnoses improved. Yet the findings were similar to those of the main analysis: no strong associations between endometriosis and the two genital anomalies were found.

Further aiming to assess the level of misclassification of endometriosis, we addressed the association between endometriosis and preterm birth. We found the expected statistically significant higher risk, similar to the findings of a previous Danish study using histology-verified information on maternal endometriosis (11). This provides some indication that the potential misclassification of endometriosis may not have a large impact. Moreover, we expect to have information on the most severe cases of endometriosis, and the findings might not be generalized to women with milder endometriosis.

Until quite recently, the risks of adverse pregnancy outcomes for women with endometriosis were largely unknown. Currently, some evidence points toward a higher risk of several pregnancy and birth complications, including preterm birth (7–11), although conflicting results exist (13–15). The hypothesis of a possible association between endometriosis and genital anomalies is rather new, and the possible underlying mechanisms are speculative. Endometriosis is an estrogen-dependent disease with multiple pathophysiologic mechanisms; local and systemic chronic inflammation, alterations in prostaglandin metabolism, and defective placentation resulting in poor placental function have been suggested (15). The most consistently reported risk indicators for cryptorchidism and hypospadias are low birth weight and preterm birth (35,36), indicating an important role of placental dysfunction (37).

In early pregnancy, human chorionic gonadotropin (hCG) from the placenta is essentially responsible for stimulating testosterone synthesis from the fetal testes (38, 39). The critical role of a balanced ratio of androgens and estrogens is well known in the delicate formation of the fetal genitals as well as in the process of testicular descent (40, 41). A relation between endocrine disruption in women with endometriosis and male genital anomalies could thus be speculated, in line with previous hypotheses that estrogenic endocrine-disrupting chemicals during pregnancy may disturb male sexual development and function (42, 43). During the last decades the research on male reproductive consequences of environmental factors has been extensive, and the hypothesis has been widely discussed (44, 45) and remains contentious. Thus, various plausible underlying mechanisms between maternal endometriosis and the male genital anomalies, cryptorchidism, and hypospadias may exist, but our findings do not provide a strong indication of such an association. We could not corroborate the findings from the only previous study on this subject (15).

In summary, based on more than 1 million births, we found no evidence that maternal endometriosis increases the risk of hypospadias. A possible tendency toward a slightly

higher risk of cryptorchidism was indicated, and future studies are needed to explore this association further.

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