Endometriosis and pregnancy complications: a Danish cohort study

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Objective: To study the association between endometriosis and risk of pre-eclampsia, cesarean section, postpartum hemorrhage, preterm birth, and small for gestational age (SGA), in a large Danish birth cohort, while taking fertility treatment into account.
Design: Population-based study.
Setting: Not applicable.
Patient(s): A total population of 82,793 singleton pregnancies from the Aarhus Birth Cohort (1989 through 2013); 1,213 women had a diagnosis of endometriosis, affecting 1,719 pregnancies.
Intervention(s): None.
Main Outcome Measure(s): Pre-eclampsia, cesarean section, postpartum hemorrhage, preterm birth, and SGA.
Result(s): Endometriosis was associated with an increased risk of preterm birth (adjusted odds ratio [AOR] 1.67, 95% confidence interval [CI] 1.37–2.05), with the risk being highest for very preterm birth (AOR 1.91, 95% CI 1.16–3.15). Compared with unaffected women, women with endometriosis also had an increased risk of pre-eclampsia (AOR 1.37, 95% CI 1.06–1.77) and cesarean section (AOR 1.83, 95% CI 1.60–2.09). Assisted reproductive technology did not explain these findings. No association was found between endometriosis and postpartum hemorrhage or SGA.
Conclusion(s): Women with endometriosis were at increased risk of pre-eclampsia, preterm birth, and cesarean section, irrespective of use of assisted reproductive technology. (Fertil Steril® 2017;107:160–6. ©2016 by American Society for Reproductive Medicine.)
Key Words: Assisted reproductive technology, cesarean section, endometriosis, pre-eclampsia, preterm birth

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Endometriosis is a chronic gynecologic disorder defined by ectopic occurrence of endometrium-like (endometriotic) tissue, which causes local inflammation with pelvic pain and infertility. The true prevalence is unknown but has been estimated to 10% in women of reproductive age (1).

Because of abnormalities in the inner myometrium (2), endometriosis has been linked to defective deep placentation and a series of obstetric complications (3). Further, proinflammatory and angiogenic changes in the ectopic endometrium (4, 5) may overlap with mechanisms associated with preterm birth (5). The potential association between endometriosis and adverse pregnancy outcome has received increasing attention (6–16), but the results remain inconclusive. Some studies indicate no association or a lower risk of adverse pregnancy outcome with endometriosis (9, 11–13,16), whereas others have reported that women with endometriosis have a higher risk of preterm birth (6, 7, 15), pre-eclampsia (6), antepartum hemorrhage (6), cesarean section (6, 13), stillbirth (14), and having a child born small for gestational age (SGA) (7).

This discrepancy between findings may be due to the different methods used, potential lack of adjustments for confounders, small sample sizes (7–9, 12, 13, 16), or a lack of exposure and/or outcome validation (6, 15). Additionally, the exposure assessment differs greatly between studies; the major variants of endometriosis are addressed both separately (7, 8, 13) and as a single disease entity (6, 9, 14), the severity of disease lacks assessment (6–9, 13, 14), and the potential coexistence of adenomyosis is not addressed (6–9, 11–14). Further, only a few studies take the extended

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use of assisted reproductive technology (ART) among women with endometriosis (17) into account, which in itself may be a risk factor for adverse pregnancy outcomes (18). Finally, the effect of treatment before pregnancy is rarely addressed (8).

We aimed to investigate the association between endometriosis and pregnancy complications in a large Danish pregnancy and birth cohort, taking ART into account, while validating the clinical diagnosis of endometriosis histologically.

MATERIALS AND METHODS

Study Population

We performed a population-based study using data from the Aarhus Birth Cohort, the largest European birth cohort, established in 1989 (19). All pregnant women attending routine antenatal care at the Department of Obstetrics and Gynecology, Aarhus University Hospital were invited to participate (19). Around gestational week 12 to 16, women were asked to complete questionnaires with information on lifestyle and sociodemographic and health-related characteristics before and during pregnancy. Immediately after delivery, the responsible midwife provided information on course of delivery and state of the newborn, on structured coding sheets. A research midwife further validated the data.

We identified women giving birth to a singleton child between September 1, 1989 and December 31, 2013. By using each individual's unique Civil Registration Number, we linked information from the Aarhus Birth Cohort with the Danish National Patient Registry (20), the Danish Medical Birth Registry (21), the Danish National Pathology Registry and Data Bank (22), and the Danish IVF-Registry (23). The Danish National Patient Registry holds data on all hospital admissions in Denmark since 1977, and outpatient hospital contacts since 1995, classified according to the International Classification of Diseases (ICD), 8th revision until the end of 1993, and the 10th revision thereafter (20). The Danish Medical Birth Registry is a nationwide registry with information on pregnant women and their offspring since 1973 (21). The Danish National Pathology Registry and Data Bank holds information on pathology specimens analyzed in Denmark, dating back to the 1970s (22). The IVF-Registry is available from 1994 and onward and holds information on all assisted reproductive treatments (23).

When established in 1989, the Scientific Ethical Committee approved the Aarhus Birth Cohort. Informed consent was obtained from all participating women at recruitment. The Danish Data Protection Agency and the Danish National Board of Health approved the present study (J. no. 2013-41-2563 and file no. 3-3013-1017/1/).

Exposure Assessment

We identified all women with a primary or secondary diagnosis of endometriosis, using the relevant ICD-8 and ICD-10 codes (ICD-8: 625.3*; ICD-10: N80*) from the Danish National Patient Registry. All subtypes of endometriosis were included, and endometriosis was addressed as one disease entity. Because recent literature has shown a pronounced diagnostic delay of endometriosis (24–26), we included women diagnosed both before and after pregnancy, under the hypothesis that women who were not diagnosed until after pregnancy were also affected by the disease during pregnancy. Further, laparoscopic surgery is the most common diagnostic technique, and a diagnosis of endometriosis based on a pathological biopsy is the most valid diagnosis. Therefore, we used information from the Danish National Pathology Registry and Data Bank (22) to validate the diagnoses of endometriosis.

Covariates

Maternal characteristics were primarily obtained from the Aarhus Birth Cohort questionnaires. If possible, incomplete data from questionnaires were retrieved from the Danish Medical Birth Registry. Maternal age was defined as age in completed years at the time of pregnancy, categorized into $\leq$19, 20–24, 25–29, 30–34, and $\geq$35 years. Maternal prepregnant body mass index (BMI) was categorized according to the World Health Organization as $<$20, 20–24, 25–29, and $\geq$30 kg/m^2. Parity was categorized as nulliparous (0 births) and parous ($\geq$1 birth). Number of cigarettes smoked during pregnancy was categorized as 0, 1–9, or $\geq$10 cigarettes per day. Ethnicity was based on the place of birth, categorized as Denmark or other countries. Education level was based on number of completed years of school at the time of pregnancy. Information on ART was retrieved from the IVF-Registry and included information on all initiated treatment cycles performed before the present pregnancy.

Outcome Assessment

We investigated the following outcomes; preterm birth, SGA, postpartum hemorrhage, pre-eclampsia, and cesarean section. We defined preterm birth, as live birth before 37 completed weeks of gestation. In Denmark, all women are offered routine ultrasound scanning at the first antenatal visit, with a national acceptance rate of 80% in 1990, 93% in 1995 (27, 28), and approaching 100% since the Danish National Board of Health in 2004 issued new guidelines for prenatal screening and diagnosis (29). Gestational age was based on the date of the last menstrual period or ultrasound-based estimates from the Aarhus Birth cohort. To identify the outliers of gestational age we applied an algorithm developed by Basso and Wilcox (30). To further analyze the association between endometriosis and preterm birth, we categorized preterm birth into very preterm birth (before gestational week 32) and moderate preterm birth (gestational weeks 32–36). We also categorized preterm birth as spontaneous (spontaneous labor or preterm premature rupture of membranes) or induced (elective cesarean section, acute cesarean section before labor, or induction of labor). We defined SGA as a birth weight 2 SDs or more below the mean for gestational age, calculated separately for male and female infants, using external SDs (31). Information on cesarean section and postpartum hemorrhage was obtained from the Aarhus Birth Cohort. Cesarean section was further divided into elective or acute cesarean section; acute cesarean section defined as a cesarean section within less than 8 hours after

the decision of this mode of delivery. Postpartum hemorrhage was characterized as bleeding ≥500 mL within the first 24 hours following childbirth. The presence of pre-eclampsia was based on any diagnosis of pre-eclampsia in the Danish National Patient Registry (ICD-8: 637.03, 637.04 0,637.09, 637.10; ICD-10: O14* or O15*). The quality of the diagnosis of pre-eclampsia has previously been validated, with a positive predictive value of 74% and a specificity of 99% (32).

Statistical Analyses

Missing information. In total, 82.6% of the study population had complete information on exposure, outcome, and covariates. The proportions of missing values were as follows; gestational age, 0.1%; birth weight, 0.3%; postpartum hemorrhage, 2.3%; cesarean section, 0.8%; prepregnant BMI, 2.7%; maternal cigarette smoking during pregnancy, 0.2%; parity, 0.7%; country of birth, 0.3%; and years of school, 13.3%. Some subjects had more than one missing value. We addressed missing information by using multiple imputations. This method has been shown to yield unbiased and more precise estimates than complete case analyses, if data are missing at random. Thus the missing data can be accounted for by variables already observed (33, 34). We performed multiple imputation using chained equations, and the models fitted were logistic regression, ordered logistic regression, and predictive mean matching. Nonnormality was dealt with using multivariable fractional polynomial models. The following variables were included in the main imputation model: diagnosis of endometriosis, gestational age, birth weight, postpartum hemorrhage, pre-eclampsia, cesarean section, ART, maternal age, maternal prepregnant BMI, maternal cigarette smoking during pregnancy, maternal alcohol consumption during pregnancy, years of school, parity, maternal place of birth, calendar year of birth, Apgar score, sex of the child, birth length, and the child's head circumference at birth. All variables included in the multiple imputation model were significant predictors of one or more of the dependent variables, supporting the assumption of data being missing at random. We created 50 imputed datasets for the main analyses and checked the robustness of our results by creating 60 imputed datasets, including more covariates than in the main imputation model, and finally by comparing the results with the complete case analysis, with and without adjusting for potential confounders.

Data analyses. We used logistic regression analyses to study the association between endometriosis and the outcomes described and presented crude and adjusted odds ratios (AORs) with 95% confidence intervals (CIs). A priori we identified potential confounders using directed acyclic graphs and included the following covariates in the statistical analyses: maternal age, maternal prepregnant BMI, parity, maternal place of birth, years of school, and calendar year of childbirth. We took repeated pregnancies into account by allowing intragroup correlation, making the observations independent across clusters of the maternal Civil Registration Number.

Subanalyses were performed to check the consistency of our results. First, we repeated the analyses while only including women with a diagnosis of endometriosis before delivery. Second, we performed the same analysis on a subgroup of women with a laparoscopic verified diagnosis. Third, to attain an understanding of the underlying mechanisms regarding preterm birth, we removed all induced deliveries and repeated the analyses on preterm birth. Fourth, to further investigate the association between endometriosis and cesarean section, we excluded all pregnancies affected by pre-eclampsia, preterm birth, or SGA. Finally, to investigate the influence of ART on the association between endometriosis and adverse pregnancy outcome, we performed the analysis stratified by ART. The data were analyzed using the STATA 13 software package (StataCorp).

RESULTS

We included 83,087 singleton births with a gestational age of 24–44 weeks in the Aarhus Birth Cohort between September 1, 1989 and December 31, 2013, who were valid members of the cohort with completed questionnaires and birth records at Aarhus University Hospital. We excluded 294 cases of stillbirths. Women with endometriosis accounted for 4 (0.23%) stillbirths, compared with 290 (0.36%) among women without endometriosis. Thus, a total of 82,793 pregnancies (55,829 women) constituted the final study population. In these pregnancies, 1,213 women (2.2%) were registered with a diagnosis of endometriosis in the Danish National Patient Registry, corresponding to 1,719 pregnancies (2.1%).

In Table 1 the characteristics of the participants are presented. Women with endometriosis were on average of higher maternal age at the time of pregnancy, compared with women without the diagnoses. Further, ART was more prevalent in women with endometriosis. There were no major differences in prepregnant BMI, parity, years of school, maternal country of birth, and cigarette smoking.

Table 2 presents the main results of the association between endometriosis and adverse pregnancy outcomes. Compared with women without endometriosis, a diagnosis of endometriosis was associated with a higher risk of pre-eclampsia, preterm birth, and cesarean section. We found no association between endometriosis and SGA or postpartum hemorrhage (Table 2). The risk of preterm birth in women with endometriosis was higher for the very preterm deliveries (AOR 1.91, 95% CI 1.16–3.15), compared with moderate preterm delivery (AOR 1.64, 95% CI 1.33–2.03). Further, the risk of preterm birth associated with endometriosis decreased slightly when we excluded all induced deliveries, but it remained significant (AOR 1.46, 95% CI 1.12–1.91). Women with endometriosis were more often delivered by elective cesarean section (AOR 2.00, 95% CI 1.67–2.41). For acute cesarean section the corresponding AOR was 1.72 (95% CI 1.47–2.01). When we, in a secondary analysis, excluded pregnancies complicated by pre-eclampsia, preterm birth, or SGA, the AOR for any cesarean section decreased slightly (AOR 1.74, 95% CI 1.50–2.01).

The ORs of the associations between endometriosis and the five adverse pregnancy outcomes remained essentially the same in women who received ART, compared with women without ART (Table 3).

TABLE 1

Maternal characteristics among women with and without endometriosis in 82,793 live, singleton births in Aarhus, Denmark between 1989 and 2013.

Characteristic	Endometriosis (n = 1,719)	No endometriosis (n = 81,074)
Age (y)		
≤19	10 (0.6)	1,055 (1.3)
20–24	152 (8.8)	8,739 (10.8)
25–29	578 (33.6)	29,851 (36.8)
30–34	644 (37.5)	28,601 (35.3)
≥35	335 (19.5)	12,828 (15.8)
Missing	–	–
BMI (kg/m^2)		
≤19.9	362 (21.1)	16,605 (20.5)
20–24.9	958 (55.7)	45,650 (56.3)
25–29.9	266 (15.5)	11,915 (14.7)
≥30	105 (6.1)	4,675 (5.8)
Missing	28 (1.6)	2,229 (2.8)
Parity		
0	890 (51.8)	39,581 (48.8)
≥1	818 (47.6)	40,949 (50.5)
Missing	11 (0.6)	544 (0.7)
Years of school		
≤9	147 (8.6)	6,669 (8.2)
10–11	351 (20.4)	14,425 (17.8)
≥12	1,010 (58.8)	49,201 (60.7)
Missing	211 (12.3)	10,779 (13.3)
ART[a]		
No	1,238 (86.5)	64,967 (97.6)
Yes	193 (13.5)	1,614 (2.4)
Country of birth		
Denmark	1,527 (88.8)	69,815 (86.1)
Other	188 (10.9)	11,015 (13.6)
Missing	4 (0.2)	244 (0.3)
Smoking		
None	1,421 (82.7)	68,132 (84.0)
1–9 cigarettes/d	132 (7.7)	6,301 (7.8)
≥10 cigarettes/d	161 (9.4)	6,482 (8.0)
Missing	5 (0.3)	159 (0.2)

Note: Values are number (percentage).
[a] ART is based on 68,012 singleton live births between 1994 and 2013, with 1,431 pregnancies exposed to endometriosis and 66,581 non-exposed.

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Further, we aimed to check the sensitivity of the exposure assessment. First, we restricted our group of exposed to women diagnosed with endometriosis before pregnancy (n = 834), which resulted in higher risk estimates. Second, we used exposure information from the Danish National Pathology Registry and Data Bank, because we expected these to have higher positive predictive value of endometriosis. In the total study population, 624 women (1.1%) had a diagnosis of endometriosis based on histology, and this affected 865 pregnancies (1.0%). We observed a notable increase in the risk estimates when repeating the analyses on this subset of the study population (Fig. 1).

Finally, we checked the robustness of the imputation models, and neither of these subanalyses changed our results. Additionally, when compared with the analyses restricted to complete cases, the estimates were essentially the same.

DISCUSSION

In this large, population-based study, we found a higher risk of pre-eclampsia, preterm birth, and cesarean section in women with endometriosis, when compared with women without the disease. The estimated risks remained essentially the same when stratified by the use of ART.

Regarding preterm birth, we found the highest risk estimate for the very preterm deliveries. Our results on preterm birth are to some extent consistent with results recently found by Stephansson et al. (6). In a large Swedish registry-based study they also found a higher overall risk of preterm birth, but with the risk being highest for moderately preterm deliveries. Other studies have focused on risk of preterm birth in subgroups of endometriosis. Fernando et al. (7) reported an increased risk of preterm birth and SGA separately for women with ovarian endometrioma. Conversely, in a recent study by Benaglia et al. (13), women with ovarian endometrioma undergoing ART had no excess risk of preterm birth or SGA. However, these studies (7, 13) were limited by relatively small sample size, and the results may not be comparable with results from studies that focus on endometriosis as one disease entity.

The existing literature on the relationship between endometriosis and pre-eclampsia is conflicting. Studies have found both lower and unchanged risks (9, 11, 12), except for the study by Stephansson et al. (6) who, like us, found an association between endometriosis and risk of pre-eclampsia. Recent literature describes pre-eclampsia as a heterogonous syndrome, with early- and late-onset pre-eclampsia referring to different disease entities (35). Especially early-onset pre-eclampsia (<34 weeks' gestation) has

TABLE 2

Crude ORs and AORs with 95% CIs for pregnancy complications in women with endometriosis among 82,793 live singletons births in Aarhus, Denmark between 1989 and 2013.

	Distribution of adverse pregnancy outcome (%)			
Variable	Endometriosis (n = 1,719)	No endometriosis (n = 81,074)	Crude OR (95% CI)	AOR[a] (95% CI)
Preterm birth (<37 wk)	7.27	4.33	1.73 (1.41–2.12)	1.67 (1.37–2.05)
SGA	2.45	2.35	1.04 (0.76–1.43)	1.00 (0.73–1.37)
Pre-eclampsia	4.30	3.07	1.42 (1.10–1.83)	1.37 (1.06–1.77)
Postpartum hemorrhage	9.23	9.42	0.98 (0.82–1.16)	0.95 (0.80–1.14)
Cesarean section	24.08	14.14	1.93 (1.69–2.19)	1.83 (1.60–2.09)

[a] Adjusted for maternal age (≤19, 20–24, 25–29, 30–34, and ≤35 years), maternal prepregnant BMI (<20, 20–24.9, 25–29.9, and ≥30 kg/m^2), parity (nulliparous or parous), ethnicity (based on the place of birth, categorized as Denmark or other countries), years of school (≤9, 10–11, or ≥12 years), and year (categorized as ≤1993 or ≥1994).

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TABLE 3

Crude ORs and AORs with 95% CIs for pregnancy complications in women with endometriosis, stratified by ART, among 68,012 live singletons births in Aarhus, Denmark between 1994 and 2013.

	ART				No ART			
	Distribution of adverse pregnancy outcome (%)				Distribution of adverse pregnancy outcome (%)			
Variable	Endometriosis (n = 193)	No endometriosis (n = 1,614)	Crude OR (95% CI)	Adjusted OR[a] (95% CI)	Endometriosis	No endometriosis	Crude OR (95% CI)	Adjusted OR[a] (95% CI)
Preterm birth[b]	12.43	7.45	1.76 (1.10–2.83)	1.85 (1.15–2.99)	6.62	4.27	1.68 (1.31–2.15)	1.66 (1.30–2.11)
SGA	2.09	2.66	0.78 (0.28–2.19)	0.74 (0.26–2.10)	2.50	2.34	1.01 (0.68–1.50)	0.98 (0.66–1.46)
Pre-eclampsia	5.18	4.34	1.20 (0.61–2.38)	1.27 (0.63–2.58)	4.19	3.04	1.41 (1.06–1.89)	1.43 (1.06–1.92)
Postpartum hemorrhage	17.54	15.16	1.19 (0.79–1.79)	1.16 (0.77–1.75)	8.18	9.30	0.81 (0.66–1.01)	0.82 (0.66–1.01)
Cesarean section	38.67	22.85	2.13 (1.53–2.97)	2.36 (1.68–3.31)	22.24	13.96	1.84 (1.58–2.14)	1.80 (1.54–2.10)

[a] Adjusted for maternal age (≤19, 20–24, 25–29, 30–34, and ≤35 years), maternal prepregnant BMI (<20, 20–24.9, 25–29.9, and ≥30 kg/m^2), parity (nulliparous or parous), ethnicity (based on the place of birth, categorized as Denmark or other countries), and years of school (≤9, 10–11, or ≥12 years).
[b] <37 weeks.

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been linked to defective trophoblast invasion and fetal growth restriction (36). We found no association between endometriosis and SGA. However, we had limited power to study early- and late-onset pre-eclampsia separately.

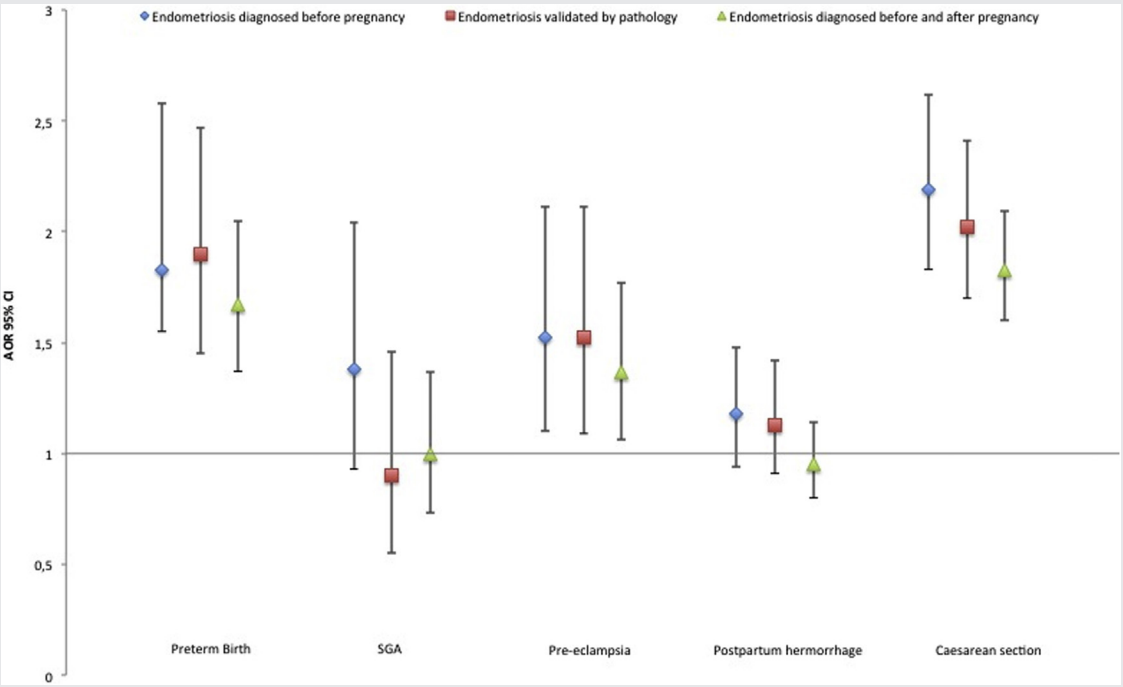
We also observed a higher risk of cesarean section, with a twofold increased risk of elective cesarean section, corroborating the findings by Stephansson et al. (6). In our study, women with endometriosis were of higher maternal age and more often conceived by ART, which could confound the results. However, despite adjustment for age and ART the results remained essentially unchanged. Furthermore, after we excluded pregnancies complicated by pre-eclampsia, preterm birth, or SGA the higher risk persisted. This indicates that the higher risk of cesarean section among women with endometriosis may be due to factors related to the disease, either biologically or psychologically. One could speculate whether women with endometriosis may choose to avoid further pelvic pain during a vaginal delivery. Thus, a cesarean delivery on maternal request may offer at least a partial explanation for the increase in elective cesarean sections among women with endometriosis.

In our study, the ascertainment of the diagnosis of endometriosis was based on registration in the Danish National Patient Registry. Because of a documented diagnostic delay from onset of symptoms to a diagnosis of endometriosis of 6–10 years (24–26), we included women diagnosed both before and after pregnancy. This decision could have induced nondifferential misclassification and attenuation of the reported association. We therefore confined the exposure to those with a diagnosis of endometriosis before pregnancy, and found an even stronger association.

The validity of the diagnoses of endometriosis in the Danish National Patient Registry remains unknown. In contrast to previous register-based studies (6, 11), we were able to corroborate the diagnosis of endometriosis in 579 pregnancies (33.7%) by information on laparoscopic biopsy from The Danish National Pathology Registry and Data Bank. When we used the histologically verified diagnosis as exposure, the results became even stronger. Advanced stages of disease among women undergoing laparoscopic surgery may be a possible explanation for the higher risk estimates observed among these women. Unfortunately, we were unable to stratify by severity because this would render strata too small for statistical inference. However, to the best of our knowledge, this is the first large study on the association between endometriosis and adverse pregnancy outcome, with knowledge on the number of histologically verified diagnoses of endometriosis. This limits any possible misclassification of disease and strengthens the validity of our study.

Endometriosis poses challenges for affected women's fertility (37), and singletons conceived by ART have a higher risk of obstetric complications (18). We therefore stratified our analysis by ART; however, this may imply some pitfalls worth considering. When seeking to assess the direct effect of endometriosis on an adverse pregnancy outcome, the use of ART can be regarded as an intermediate factor (6, 17). Because there are other possible unmeasured confounding variables that could affect both ART and the adverse

FIGURE 1



Adjusted odds ratios with 95% CIs for pregnancy complications in women with endometriosis, categorized by different exposure groups, among 82,793 live singletons births in Aarhus, Denmark between 1989 and 2013.

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pregnancy outcome, stratifying by ART may introduce bias (38). However, results remained essentially the same after stratifying by ART. The coexistence of adenomyosis and endometriosis may play a role in the development of pregnancy complications (39). Only 252 of the 1,719 pregnancies categorized as those with endometriosis had the diagnosis adenomyosis. After excluding pregnancies of women identified with adenomyosis, the results remained essentially unchanged (data not shown).

Furthermore, treatment of endometriosis may play a role in the development of pregnancy complications. Unfortunately, we were unable to assess the effect of treatment of endometriosis before conception on pregnancy outcome.

Not all eligible women accept inclusion in the Aarhus Birth Cohort, and participants might differ from nonparticipants. Because of inclusion in very early pregnancy, it is unlikely that participation depends on pregnancy outcomes, and the risk of selection bias is therefore negligible. Although large, the size of our cohort did not allow for statistical analyses of multiple pregnancies. However, the restriction to singleton pregnancies enhanced the internal validity and improved the generalizability to other cohorts of singleton pregnancies. Unfortunately we did not have the power to study stillbirth. We therefore restricted our study to include only live births and introduced proxy variables for stillbirth, newborn, and child health (preterm birth, SGA, pre-eclampsia). If endometriosis both affects women's fecundity (37) and increase the risk of fetal death (14), bias may have been introduced (40). This may have attenuated the associations found between endometriosis and pregnancy complications. However, Liew et al. (40) showed by simulation that the magnitude of this bias was small.

The underlying potential mechanism of pregnancy complications in women with endometriosis is still largely unknown. The peritoneal fluid of women with endometriosis is characterized by proinflammatory changes, with increased levels of cytokines and angiogenic factors (4), which could be a possible explanation for the higher risk of preterm birth (5). The uterine junctional zone is the site for placentation in pregnancy. Pre-eclampsia is a complex disease characterized by defect transformation of the spiral arteries at the junctional zone (3). Imaging studies have found an association between endometriosis and a thickening of this tissue (2). A local increase in uterine peristaltic activity might cause microtraumatization (41, 42) and impaired implantation (43). A higher risk of pre-eclampsia in women with endometriosis may be mediated by these factors, as may the risk of preterm delivery.

We only had information on endometriosis for those who were diagnosed in a hospital or an outpatient clinic. These women are most likely the more severe cases of endometriosis, whereas women with milder endometriosis may not have been referred from their general practitioner or gynecologist. This may limit the generalizability of our results to women with a more severe degree of endometriosis.

In summary, we found results supporting the hypothesis that endometriosis is a risk factor for pre-eclampsia, preterm birth, and cesarean section. Thus, our results strongly suggest that the obstetric risks associated with endometriosis should

be taken seriously, and further research concerning the underlying mechanisms is needed.

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