

# 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® 2016; ■: ■–■. ©2016 by American Society for Reproductive Medicine.)

**Key Words:** Assisted reproductive technology, cesarean section, endometriosis, pre-eclampsia, preterm birth

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**E**ndometriosis 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 placenta-

tion 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 pre-pregnant body mass index (BMI) was categorized according to the World Health Organization as  $<20$ , 20–24, 25–29, and  $\geq 30$  kg/m<sup>2</sup>. 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

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