ORIGINAL ARTICLE: ENDOMETRIOSIS

Association between surgically diagnosed endometriosis and adverse pregnancy outcomes

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Objective: To examine the association between surgically diagnosed endometriosis and pregnancy outcomes in subsequent pregnancies.
Design: Retrospective cohort study of women who delivered a singleton live birth from 2003 to 2013 in Ottawa, Ontario, Canada.
Setting: Tertiary level academic center.
Patient(s): Pregnant women with surgically diagnosed endometriosis were identified using International Classification of Diseases-10 codes from previous hospital admissions and were compared with pregnant women with no prior admission for endometriosis for the occurrences of adverse pregnancy outcomes.
Intervention(s): Observational study.
Main Outcome Measure(s): Gestational hypertension, preeclampsia, placenta previa, placental abruption, postpartum hemorrhage, preterm birth, low birth weight, small for gestational age, and neonatal intensive care unit admission.
Results: Among the 52,202 eligible mother-infant pairs, we identified 469 mothers with surgically diagnosed endometriosis from a previous hospital encounter. Compared with women without endometriosis, women with endometriosis were on average older and were more likely to be primiparous, have lower gravidity, have a history spontaneous abortion, conceive with assisted reproductive technology, and reside in areas with higher neighborhood income and lower proportion of immigrants. Women with endometriosis were found to have an elevated risk of placenta previa (relative risk [RR], 3.30; 95% confidence interval [CI], 1.65–5.40) and cesarean delivery (RR, 1.24; 95% CI, 1.10–1.40). After adjustment for potential confounding factors, women with endometriosis were found to have a significantly elevated risk of placenta previa compared with women without endometriosis (adjusted RR, 2.54; 95% CI, 1.39–4.64).
Conclusion(s): This study identifies baseline demographic differences between women with and without endometriosis and suggests that women affected by endometriosis have an independently elevated risk of placenta previa in pregnancy. (Fertil Steril® 2017;■: ■–■. ©2017 by American Society for Reproductive Medicine.)
Key Words: Endometriosis, pregnancy outcomes, placenta previa, caesarean delivery

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Endometriosis, a condition characterized by the presence of endometrial glands and stroma outside of the uterine cavity and diagnosed by surgery (1, 2), is a common health problem, affecting approximately 10%–15% of women of reproductive age (3). Endometriosis is linked to infertility, and current estimates suggest 30%–50% of women with endometriosis have difficulty conceiving (4–6). Despite the negative impact of endometriosis on fertility, more women with endometriosis are conceiving with the assistance of reproductive technologies (7). However, it is possible that mechanisms that interfere with fertility in women with endometriosis may also have adverse maternal and infant outcomes.

There are several reasons why endometriosis may contribute to adverse pregnancy outcomes. Aside from alterations in the uterine environment due to the regional anatomic changes, endometriosis may also be

associated with altered ovulation and oocyte production, increased inflammatory cells in the peritoneal fluid, endometrial P resistance, and inadequate uterine contractility, all of which may compromise normal embryonic development and pregnancy implantation (5–9). Research on the pathogenesis of poor pregnancy outcomes suggests that such disturbances in the peri-implantation period may perpetuate throughout the later stages in pregnancy (8, 9).

At a population level, the detection of adverse maternal and infant outcomes in observational studies generally requires large sample sizes. Several smaller studies—with sample sizes <1,000—have reported conflicting findings with respect to the presence of endometriosis and various perinatal outcomes, suggesting the possibility of reduced statistical power in some cases (10–15).

Studies with larger sample sizes have reported association with various differing adverse pregnancy outcomes. In one study (n = 1,140), women with ovarian endometrioma were found to be at increased risk of preterm birth and small for gestational age (SGA). However, in the analyses, women with endometriosis and assisted reproduction were compared with women with natural conception, so the independent effect of endometriosis from that of assisted reproductive technology was difficult to ascertain (16). In another study (n = 30,284), endometriosis was associated with pregnancy loss and stillbirth, after adjustment for age, gestational age, birth weight, and body mass index. However, this study did not control for the effect of assisted reproduction as a potential confounder (17). One study of nulliparous women (n = 205,640) did not find association between endometriosis and preeclampsia after adjustment for various confounders. However, preeclampsia was the only outcome studied (18). One large national Swedish study (n = 1,442,675) reported associations with preterm birth, preeclampsia, antepartum bleeding, and cesarean section, after adjustment for age, smoking, body mass index, parity, years of formal education, and year of birth. In further analyses, the outcome of preterm birth was stratified by whether the woman underwent assisted reproduction, but this stratification was not performed for other reported outcomes (6).

Thus, despite a number of reports on the association between endometriosis and various adverse pregnancy outcomes, the published literature in this area is difficult to interpret, with conflicting findings (10–12, 16–22). Some of these studies may have been limited by smaller sample size, inappropriate comparison groups, or lack of consideration for some potentially important confounders. Furthermore, most of the studies did not document whether included patients had diagnostic laparoscopy to confirm the presence of endometriosis, which may impact the strength of the association between endometriosis and pregnancy outcomes. Given the prevalence of endometriosis and the clinical significance of adverse pregnancy outcomes, we conducted a large Canadian cohort study to investigate the association between endometriosis and several important maternal and fetal outcomes with the consideration of clinically relevant confounders.

MATERIAL AND METHODS
Study Population and Record Linkage
We obtained approval from the Ottawa Hospital Research Ethics Board before the commencement of this study. Women who had a singleton live birth at the Ottawa Hospital between January 1, 2003, and December 31, 2013, were identified from the Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD). In cases where more than one birth record was available for a patient, only information from the first record was included in the analysis. The birth records for these women were linked by healthcare numbers to surgical hospital records to ascertain their surgical history. Women with a history of fibroids (International Classification of Diseases [ICD]-10 code: D25) were excluded. The included women were then divided into those with surgically diagnosed endometriosis as captured by the ICD (ICD-10 code: N80) and those without surgically diagnosed endometriosis. Maternal records were linked to infant records using the maternal-infant chart number in the CIHI-DAD, so that the associations between maternal characteristics and infant outcomes could be analyzed.

Baseline Characteristics
Baseline characteristics in this study included maternal age, neighborhood income, immigrant population, gravidity, parity, previous spontaneous and therapeutic abortions, use of assisted reproductive technology, chronic hypertension (ICD-10 code: I10, I11, I12, I13, I15), preexisting diabetes (ICD-10 code: E10, E12, E13, E14), and infant sex.

The relationship between endometriosis and socioeconomic status (6, 23), and the relationship between adverse perinatal outcomes and socioeconomic status (6, 24), have previously been reported in the literature. As such, markers of socioeconomic status were included as potential confounders. The two socioeconomic status measures— neighborhood income and immigration population—were based on the mother's resident dissemination area determined by patient postal code. A dissemination area is a small, relatively stable geographic unit composed of one or more adjacent dissemination blocks, defined by Statistics Canada (25). It is the smallest standard geographic area for which all census data are disseminated. Neighborhood income was defined as per person equivalent, a household size-adjusted measure of household income, based on 2006 census summary data, in quintiles. Neighborhood immigration population was defined as proportion of immigrant population, again based on 2006 census summary data, in tertiles.

Main Outcome Measures
Maternal outcomes of interest included gestational hypertension and preeclampsia (ICD-10 code: O11, O13, O14, O15), placenta previa (ICD-10 code: O44), placental abruption (ICD-10 code: O45), and postpartum hemorrhage (ICD-10 code: O72). Infant outcomes of interest included preterm birth (before 37 completed weeks of gestation), low birth weight (<2,500 g), SGA, defined by either third or fifth percentiles