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Pregnancy outcomes among women with endometriosis and fibroids: registry linkage study in Massachusetts

Leslie V Farland[1,2], **Judy E Stern**[3], **Chia-ling Liu**[4], **Howard J Cabral**[5], **Charles C. Coddington III**[6], **Hafsatou Diop**[4], **Dmitry Dukhovny**[7], **Sunah Hwang**[8], **Stacey A Missmer**[9,10]

[1)]Department of Epidemiology and Biostatistics, Mel and Enid Zuckerman College of Public Health, University of Arizona

[2)]Department of Obstetrics and Gynecology, College of Medicine- Tucson, University of Arizona

[3)]Department of Obstetrics and Gynecology, Dartmouth-Hitchcock, Lebanon, NH

[4)]Massachusetts Department of Public Health, Bureau of Family Health and Nutrition, Boston, MA

[5)]Department of Biostatistics, Boston University School of Public Health, Boston, MA

[6)]Department of Obstetrics and Gynecology, Carolinas Medical Center/Atrium Health, Charlotte, NC

[7)]Department of Pediatrics, Oregon Health & Science University, Portland, Oregon

[8)]Department of Pediatrics, Section of Neonatology, University of Colorado School of Medicine, Aurora, CO

[9)]Department of Obstetrics, Gynecology, and Reproductive Biology, College of Human Medicine Michigan State University, Grand Rapids, MI

[10)]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA

Abstract

Background: Endometriosis and uterine fibroids are common gynecologic conditions associated with greater risk of infertility. Prior research has suggested that these conditions are associated with adverse pregnancy outcomes, potentially due to increased utilization of fertility treatments.

Objective: Therefore, our objective was to investigate whether women with a history of endometriosis or fibroids had a greater risk of adverse pregnancy outcomes and whether this risk varied by infertility history and fertility treatment utilization.

Materials and Methods: Deliveries (2013–2017) from Massachusetts vital records were linked to assisted reproductive technology (ART) data, hospital stays, and All-Payers Claims Database (APCD). We identified endometriosis and fibroids diagnoses via APCD before index delivery. Adjusted relative risks (aRR) for pregnancy complications were modeled using generalized

Address for correspondence: Dr. Leslie V. Farland, University of Arizona, 1295 N Martin Ave, Drachman Hall A236, PO Box 245211, 85724, Tel: 520-626-8025.

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estimating equations with a log link and Poisson distribution. The influence of subfertility/infertility and ART was also investigated.

Results: Among 91,825 deliveries, 1,560 women had endometriosis and 4,212 had fibroids. Approximately 30% of women with endometriosis and 26% of women with fibroids experienced subfertility or infertility without utilizing ART, with 34% of women with endometriosis and 21% of women with fibroids utilizing ART for index delivery. Women with a history of endometriosis or fibroids were at a greater risk of pregnancy induced hypertension/ preeclampsia/ eclampsia (RR Endometriosis:1.17; RR Fibroids:1.08), placental abnormalities (RR Endometriosis:1.65; RR Fibroids:1.38), and caesarean section (RR Endometriosis:1.22; RR Fibroids:1.17) compared to women with no history of those conditions. Neonates of women with a history of endometriosis or fibroids were also at a greater risk of preterm birth (RR Endometriosis:1.24; RR Fibroids:1.17). Associations between fibroids and low birthweight varied by fertility status/ART (p-heterogeneity=0.01) and were stronger among non-infertile women.

Conclusion: Endometriosis or fibroids increased the risk of adverse pregnancy outcomes possibly warranting differential screening or treatment.

Condensation:

Endometriosis and/or fibroids may increase the risk of adverse pregnancy outcomes possibly warranting differential screening or treatment.

Keywords

Endometriosis; epidemiology; infertility; adverse pregnancy outcomes

Introduction:

Endometriosis and uterine fibroids are common gynecologic disorders; endometriosis burdens approximately 10% of reproductive aged women[1, 2] and fibroids are estimated to affect 20–40% of women during their reproductive years[3] and between 2–11% of pregnant women[4–6]. Recent genome-wide association studies (GWAS) have suggested that fibroids and endometriosis share common genetic origins,[7] and observational epidemiologic studies support the association between these conditions.[7–9] Moreover, both of these conditions are associated with increased risk of infertility[10, 11], which has led to increasing interest into the association between these gynecologic conditions and adverse pregnancy outcomes.

Investigating the association between endometriosis, fibroids, and risk of adverse pregnancy outcomes can be challenging given the rarity of many adverse pregnancy outcomes[12]. One goal, therefore, is to find data with sufficient sample size to yield adequate statistical power. Previous meta-analyses and systematic reviews have suggested that women with endometriosis may be at greater risk of placenta previa, cesarean delivery, and preterm birth compared to pregnancies among women without endometriosis[13–16]. Similarly, pregnancies to women with fibroids have been found to have an elevated risk of preterm birth, placental abnormalities, and cesarean delivery[17, 18]. However, the majority of the research to date has come from clinical studies of women undergoing fertility treatment or has been restricted to a single surgical practice that may be prone to issues of external and internal validity.

These studies are unable to disentangle the influence of the gynecologic condition from the influence of the fertility treatment, as fertility treatment has been associated with risk of many adverse pregnancy outcomes[19, 20]. Additionally, comparisons among patients within these settings may underestimate the influence of gynecologic conditions on adverse pregnancy outcomes as women with subfertility or other gynecologic conditions, who make up the patient population of these clinics, may also independently be at greater risk of adverse outcomes[9, 21, 22].

To overcome some of these limitations, we used a large database developed through data linkage in Massachusetts to investigate whether women who have a history of endometriosis and/or fibroids have greater risk of adverse maternal outcomes, such as gestational diabetes, preeclampsia, and placental abnormalities, and greater risk of adverse pregnancy outcomes such as low birthweight, preterm birth, small for gestational age, cesarean delivery, and prolonged neonatal hospital stay. We also investigated whether there were differences in the risk for adverse pregnancy outcomes by subfertility and fertility treatment utilization.

Materials and methods:

Data from the 1) Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS), 2) Massachusetts Pregnancy to Early Life Longitudinal (PELL) data system and 3) Massachusetts All Payers Claims Database (APCD) were linked for this analysis. Specifically, ART cycles performed in the state of Massachusetts between 2004–2017 from the SART CORS were linked to delivery records and thence to delivery hospital discharges in the PELL data system, as has been described in detail previously[23]. The study had IRB approvals from the Massachusetts Department of Public Health, Boston University, and Dartmouth-Hitchcock Health.

We developed the Massachusetts Outcome Study of Assisted Reproductive Technology (MOSART) database by linking SART CORS deliveries from July 1, 2004 to December 31, 2017 to birth certificates and fetal death records using mother's first and last name, father's last name, mother's date of birth, and date of delivery. For 2004–2017 the linkage rates were 91.5% overall and 94.9% for those in which both ART cycle patient zip code and treatment clinic were located in Massachusetts[23].

As has been described previously[24, 25], we obtained APCD for all available claims to women who delivered between January 1, 2013 and December 31, 2017. The APCD includes insurance claims from public and private insurance payers in Massachusetts. MOSART data from 2013 through 2017 were linked to the APCD under an additional Memorandum of Understanding among the Center for Health Information and Analysis (CHIA) that maintains and houses APCD, Massachusetts Department of Public Health (MDPH), and project PIs. Information from the MOSART database was submitted to CHIA for linkage using the member eligibility (ME) file. For the mother's linkage, we included information on date of birth, first name, last name, and zip code. For the neonate's linkage, we included infant's date of birth, first name, last name, sex, and zip code. Upon obtaining the ME identifiers, CHIA matched and then extracted the APCD non-Medicaid (MassHealth)

medical claim records for the linked mothers and children and sent these de-identified data back to MDPH.

Exposures:

Endometriosis and uterine fibroids were the main exposures of interest and were categorized based on ICD9 and ICD10 codes reported to APCD (Endometriosis: N80.1-N80.9, 617.1–617.5, 617.8–617.9; Fibroids: D25.0-D25.2, D25.9, 218.0–218.2, 218.9). Women were considered as having a history of endometriosis and/or fibroids prior to index delivery if their APCD service date for the condition was on or before the date of index delivery. In sensitivity analyses, the association between pelvic pain presentation (625.0, 625.3, 625.9, N94.1, N94.5, N94.6, N94.89, R10.2) and adverse pregnancy outcomes was investigated. Adenomyosis was also investigated (ICD 9 617.0; ICD 10 N80.0), however the prevalence was extremely low to study (n=62 deliveries), suggesting under-investigation and diagnosis of this gynecologic disorder.

Outcomes:

The major outcomes of interest were (1) maternal outcomes (gestational diabetes, gestational hypertension/ preeclampsia/eclampsia, cesarean delivery, and placental abnormalities); (2) infant outcomes (small for gestational age status, low birth weight, prematurity, and prolonged neonatal hospital stay); and (3) neonatal conditions (conditions of infectious disease, cardiovascular, respiratory, gastrointestinal/nutritional, neurologic, and hematologic systems).

Information on hypertension during pregnancy, gestational diabetes, and placental abnormalities was identified in PELL from either the birth certificate or the hospital discharge delivery record and pre-delivery (within 280 days before delivery) ICD 9 and 10 codes (642, O11, O13-O16 for pregnancy-related hypertension; 648.8, O24.4, O24.9 for gestational diabetes; 641.0–641.2, 663.5, 667.0, 762.1, O45, P02.1, O43.21, O44, O69.4 for placental abnormalities). Information on cesarean delivery was from the birth certificate.

A birthweight Z-score was calculated as the standard deviation (SD) score of the value for each individual from the mean value of the Massachusetts reference population divided by the SD for that reference population[26]. We generated gender-, race/ethnicity-, and gestation length-specific birthweight means and SDs using MA data for all live births from 1998 to 2017. Information on birthweight was obtained from the birth certificates. We defined low birthweight as <2500 grams. Information on length of gestation was based on clinical estimates of first-trimester ultrasound or last menstrual period and was derived from the birth certificate. Any live-born infant with a Z-score below the 10th percentile was considered small for gestational age. Preterm birth was defined as gestational length of <37 weeks. Information on prolonged neonatal hospital stay was determined from the birth certificate and infant hospital discharge data. Prolonged stay was defined as >3 days for vaginal delivery or >5 days for cesarean delivery and was limited to deliveries in which gestational age was ≥35 weeks, and with known data on mode of delivery. As described previously[19], conditions were grouped by system based on ICD 9 and 10 codes: infectious disease, cardiovascular, respiratory, gastrointestinal and/or nutritional, neurologic,

and hematologic and were restricted to live born infants in 2013–2016 to allow capture of conditions up to one-year after birth.

Subfertility, Infertility, and ART utilization:

Deliveries were classified as having utilized ART if the delivery was linked to an ART cycle in the SART CORS database. Deliveries were classified as "subfertile" as defined by our group previously,[27] if they met one of the following criteria: 1) indicated infertility treatment on the birth or fetal death certificate, 2) utilized an ICD code for infertility (ICD codes 628 and V230; ICD 10 O09.00-O09.03 and N97.0-N97.9) during a prior hospitalization, 3) had a prior delivery with either an indication of infertility treatment or linkage to SART CORS,. Deliveries were considered "infertile" if the delivery had a prior APCD outpatient or inpatient claim with provider-confirmed diagnosis of infertility. Deliveries were classified as "non-infertile" if they did not fall into any of the other categories.

Covariates:

Information on maternal age, race/ethnicity, education, maternal pre-pregnancy body mass index (BMI), and plurality was obtained from the birth certificates. Information on maternal chronic hypertension and chronic diabetes was determined by combining information from birth certificates and hospital discharge records.

Statistical Analyses: Generalizing estimating equations (GEE) with a log-link and a Poisson distribution were used to account for multiple deliveries by the same women. These models estimated relative risk ratios (RR) and 95% confidence intervals (CI) and were adjusted *a priori* for mother's age (continuous), pre-pregnancy BMI (<25, ≥25 kg/m^2, unknown), race/ethnicity (non-Hispanic White, other race/ethnicity, unknown), maternal education (high school and/or some college, completed college, unknown), plurality (singleton, multiple), birth year (2013–2017 ordinal categorical calendar years), maternal history of chronic hypertension, maternal history of chronic diabetes, and gestational age (continuous). Analyses where the main exposure was endometriosis were additionally adjusted for fibroids and vice versa. Effect modification by fertility status/ART utilization was investigated by stratifying births into "Non-infertile," "Subfertile or infertile," and "ART." Likelihood ratio tests comparing multivariable models with and without an interaction term between the exposure and fertility status was used to test for heterogeneity. Given that endometriosis and fibroids are challenging to diagnose leading to diagnostic delays and that pathophysiology of both conditions may vary by sub-phenotypes defined by presenting symptoms[8, 28], sensitivity analyses investigated the association between pelvic pain diagnosed prior to index delivery (ICD-9: 6250, 6253, 6259; ICD-10: N941, N945–6, N9489, R012) and adverse pregnancy outcomes. In accordance with guidelines from CHIA we suppressed any counts that were less than 11. Analyses were performed in SAS software 14.3 (SAS Institute, Cary NC).

Results:

In total there were 91,825 women with deliveries between October 1, 2013 and December 31, 2017 in Massachusetts for whom we had APCD data. Of those women 1,560 had

a history of endometriosis (1.7%) and 4,212 had a history of fibroids (4.6%) and 287 women had both endometriosis and fibroids (0.3%) (Table 1). Women diagnosed with endometriosis were more likely to be non-Hispanic white (79%) compared to women with fibroids (66%) and slightly more than women with history of neither endometriosis nor fibroids (75%). Women with endometriosis or fibroids were more likely to have multiples (endometriosis:5.4%, fibroids:3.9%, neither endometriosis nor fibroids: 2.3%). Women with endometriosis or fibroids were more likely to be subfertile/infertile (endometriosis: 30%, fibroids: 26%, neither endometriosis nor fibroids: 13%) or to utilize ART to conceive the index delivery (endometriosis: 34%, fibroids: 21%, neither endometriosis nor fibroids: 7%). Among deliveries which utilized ART, we observed similar prevalence of multiples among groups (Endometriosis ART:12.8%, Fibroids ART:12.5%, Neither endometriosis nor Fibroids ART:13.1%).

Women with a history of endometriosis diagnosis had a greater risk of adverse maternal outcomes including, pregnancy induced hypertensive disorder (hypertension/preeclampsia/eclampsia, RR: 1.17, 95% CI: 1.03–1.33), caesarean delivery (RR: 1.22, 95% CI: 1.15–1.29), and placental abnormalities (RR: 1.65, 95% CI:1.33–2.06) (Table 2). The association with cesarean delivery remained consistent in deliveries restricted to primiparous women. Deliveries to women with a history of endometriosis were also at greater risk of low birthweight (RR:1.23, 95% CI:1.07–1.42) and preterm birth (RR:1.24, 95% CI:1.09–1.41). When investigating adverse neonatal conditions, neonates born to women with a history of endometriosis were at greater risk of respiratory conditions. The association between endometriosis and risk of placental abnormalities varied by fertility history (p-value, test for heterogeneity: 0.02) (Supplemental Table 1) and remained elevated, but was no longer statistically significant when restricted to non-infertile women (RR:1.25, 95% CI:0.74–2.04). We observed no difference in the association between endometriosis and risk of other adverse maternal or pregnancy outcomes when stratified by history of subfertility/infertility or ART usage to conceive the index delivery (Supplemental Table 1; all p-values, test for heterogeneity >0.05).

We observed that women with a history of fibroids had a greater risk of caesarean delivery (RR: 1.17, 95% CI: 1.13–1.21) and of placental abnormalities (RR: 1.38, 95% CI:1.19–1.60) (Table 3). The association between fibroids and risk of cesarean delivery remained consistent in deliveries restricted to primiparous women. Deliveries to women with a history of fibroids were at greater risk of preterm birth (RR:1.17, 95% CI:1.07–1.29) but not low birthweight (RR: 1.09, 95% CI: 0.98–1.20). However, the association between fibroids and risk of small for gestational age (p-value, test for heterogeneity=0.03) and low birthweight varied by history of subfertility/infertility or ART usage to conceive the index delivery (p-value, test for heterogeneity=0.01) (Supplemental Table 2). The association between fibroids and risk of small for gestational age (RR: 1.09, 95% CI: 0.93–1.28) low birth weight (RR: 1.29, 95% CI:1.10–1.52) was strongest among non-infertile women and attenuated among subfertile/infertile women and women who utilized ART for the index delivery. Neonates born to mothers with a history of fibroids were more likely to have cardiovascular conditions (RR: 1.29, 95% CI: 1.06–1.55), respiratory conditions (RR: 1.12, 95% CI:1.04–1.20), and GI/nutritional conditions (RR: 1.19, 95% CI: 1.05–1.34).

In sensitivity analyses investigating the association between pelvic pain and adverse maternal and pregnancy outcomes, we observed that women with a history of pelvic pain were at greater risk of cesarean delivery (RR:1.10, 95% CI:1.07–1.12), placental abnormalities (RR:1.15, 95% CI:1.03–1.27), preterm birth (RR:1.14, 95% CI:1.08–1.21) and respiratory conditions of the neonate (RR:1.08, 95% CI:1.03–1.13) (Supplemental Table 3).

Discussion:

Principal Findings:

Overall, we observed that deliveries to women with a history of endometriosis diagnosis or uterine fibroids were at greater risk of adverse maternal and delivery outcomes compared to pregnancies to women with a history of neither of these conditions. Specifically, women with either endometriosis or fibroids were at greater risk of pregnancy induced hypertension/preeclampsia/eclampsia, cesarean delivery, placental anomalies, and preterm birth. Neonates born to women with a history of endometriosis (regardless of fertility) or fibroids (but only among those who were non-infertile) were more likely to be low birthweight. Neonates born to mothers with a history of either endometriosis or fibroids were more likely to have respiratory conditions. History of pelvic pain also was associated with greater risk of cesarean delivery, placental anomalies, preterm birth, and respiratory conditions of the neonate, but not with pregnancy induced hypertension/preeclampsia/eclampsia or low birthweight.

Results:

Endometriosis and fibroids may influence pregnancy outcomes through a number of potential mechanisms[13, 17, 18, 29, 30]. Prior research has suggested that women with endometriosis have higher levels of local and systemic inflammation[31–33] that may influence risk of some pregnancy outcomes including preterm birth and pregnancy induced hypertension/preeclampsia/eclampsia[34, 35]. Issues with deficient uterine contractility[36], as well as placentation have also been hypothesized to be pathways to influence fetal growth and placentation[37]. Fibroids may directly influence placentation and the uterine cavity depending on their size, sub-phenotype, and placement, which may contribute to adverse pregnancy outcomes[38]. Moreover, previous researchers have hypothesized that myomas may decrease flexibility of the uterus, damage the interface between the uterus and placenta, and make the uterus less responsive to oxytocin[39, 40].

We observed a modest association between history of endometriosis (RR:1.18) and history of fibroids (RR:1.09) and risk of hypertensive disorders of pregnancy (pregnancy induced hypertension/preeclampsia/eclampsia). For endometriosis, this finding is consistent with findings from a recent meta-analysis of 24 studies that observed a modest association between endometriosis and risk of hypertensive disorders of pregnancy when combining all studies (Summary OR=1.21)[14] and from a recent large, prospective cohort study[30].

We also observed that deliveries to women with endometriosis or uterine fibroids had a greater risk of cesarean delivery. An increased risk of cesarean delivery among women

with endometriosis has been consistently demonstrated in meta-analyses[14, 15] and has been shown to be found across both spontaneously conceived and ART conceptions,[14] which is consistent with findings from our study. This again may be related to issues of uterine contractility among women with endometriosis. However, further research is needed to disentangle potential causal physiology from the more highly medicalized access to care among women who have successfully achieved endometriosis diagnosis[1, 28]. Deliveries to women with a history of fibroids have also consistently been associated with elevated risk of cesarean delivery[5, 17, 41–43]. The “Right from the Start Study” sought to disentangle the causal association between fibroids and risk of cesarean delivery by having all participants undergo ultrasound during the first trimester; they observed that women with fibroids had a 27% greater risk of cesarean delivery compared to women without fibroids, which attenuated after adjustment for BMI and was strongest among women with larger total tumor volume[6]. The presence of other adverse pregnancy outcomes may influence risk of cesarean delivery among this population, as may the fact that women who successfully achieve a diagnosis for these conditions may be overmedicalized relative to those who do not. Of note, we did not observe a difference in risk of cesarean delivery by history of infertility or ART utilization for women with fibroids or endometriosis.

Women with endometriosis and women with a history of fibroids were at greater risk of placental abnormalities including placental abruption, placenta previa, vasa previa, and placental accreta compared to women never diagnosed with either of these gynecologic conditions. In the literature, there has been a consistent association between endometriosis and risk of placenta previa[14, 15, 37]. It has been hypothesized that this elevated risk was influenced by fertility treatment utilization among women with endometriosis, however findings from a prior meta-analyses suggest that risk of placental abnormalities is elevated in both non-infertile deliveries and deliveries that utilized fertility treatment[14]. In our stratified analyses (Supplemental Table 1), we observed differences in the association between endometriosis and placental outcomes by ART history and subfertility/infertility status (P-value:0.02). Among ART deliveries, both women with endometriosis (10.1%) and women without endometriosis (6.1%) had similarly elevated risks of placental abnormalities in multivariable adjusted models (RR:1.01). Among non-infertile women, women with endometriosis (2.9%) had a greater risk of placental abnormalities compared to women without endometriosis (2.4%) (RR:1.25), however risks in both groups of non-infertile women were lower than risks among women who utilized ART. Consistent with our findings, women with fibroids have also been observed to have greater risk of placental abruption and placenta previa[5, 17, 18, 42], however this finding has not been consistent across all studies[39, 41]. Previous research on this topic has hypothesized that myoma location and size may influence risk, however our database did not contain the sub-phenotypic details necessary to test this in the present analysis.

We observed a 24% increased risk of preterm birth for pregnancies to women with a history of endometriosis and 17% increased risk of preterm birth for pregnancies to women with fibroids. A meta-analysis of 12 cohort studies found that pregnancies to women with endometriosis had a 49% greater risk of preterm birth (95% CI: 1.30–1.70)[44]. Risk of preterm birth has also been consistently seen in studies of uterine fibroids,[18, 45] with effect sizes ranging from RR=1.3[17] to 2.5[40], with recent studies suggesting an association with

extreme preterm birth (22–27 weeks gestation)[39]. We observed an association with low birth weight for women with endometriosis regardless of fertility status. For fibroids, in stratified analyses (Supplemental Table 2), we observed that an association with low birth weight (RR:1.29) and small for gestational age (RR:1.09) that was strongest among non-infertile women. However, the magnitude of the association was greater for low birth weight, indicating that our results are most likely influenced by the risk of preterm birth. That no association between fibroids and low birthweight was observed among subfertile/infertile deliveries or deliveries that utilized fertility treatment may suggest that the influence of fibroids on low birth weight is minimized or masked when restricted to a population already at greater risk for low birth weight[9, 27].

Clinical Implications:

Women with a history of endometriosis and fibroids may have a greater risk of certain adverse pregnancy outcomes compared to women without a history of these conditions. Additional research is needed to investigate whether pregnant women with a history of endometriosis and/or fibroids benefit from increased screening or intervention during pregnancy before these findings can be used in clinical settings.

Research Implications:

Future research should also strive to recruit large datasets with detailed information on both endometriosis and fibroids type and severity, as well as information on prior treatment of these gynecologic conditions.

Strengths and Limitations:

While this study has many strengths including its large sample size and utilization of information from vital records and medical claims, we must also recognize its limitations. There is a possibility of misclassification of endometriosis and fibroids. The prevalence of endometriosis (1.7%) and fibroids (4.6%) in our sample is lower than the expected population prevalence for these conditions across a women's lifetime.[2] However, this prevalence is consistent with population-based estimates of endometriosis[46] and with prevalence at IVF documented in SART CORS.[47] This is to be expected as our sample is restricted to women who achieved live birth and therefore, represents a younger population than the full lifetime-prevalence estimates for either endometriosis or fibroids. Further, within this live birth population, severe infertility -related endometriosis and fibroid subtypes may not be captured. Additionally, we restricted our definition to women who were diagnosed prior to delivery and so diagnoses after delivery were not captured. As with all linkage studies, women who delivered in Massachusetts but who received care for endometriosis or fibroids outside of Massachusetts or whose claims did not adequately document the condition, would be misclassified. Additionally, there may be women in our comparison group who have undiagnosed endometriosis or fibroids, however, we would expect the influence of these women to be minimal (and toward the null) given the large number of pregnancies that are truly without gynecologic diseases[48]. Moreover, registry data has limited information on patient characteristics, such as smoking history and body mass index, which may serve as potential confounding factors[49]. Our analyses do not incorporate information on endometriosis and fibroid sub-phenotypes, nor do we have information on

treatment of these disorders that may mediate their association with pregnancy outcomes. As expected from prior research from our group, ART pregnancies have an elevated risk of adverse pregnancy outcomes[19, 20, 50] that may be partially attributed to multiples. While we observed a similar prevalence of multiples in deliveries that utilized ART among women with endometriosis, fibroids, and neither condition, and plurality was controlled for in the analysis, we are not able to rule out the influence of vanishing twins which may modify risk[51].

Conclusion:

In summary, this study builds off prior research that suggests that women with endometriosis or fibroids may be at an elevated risk of pregnancy induced hypertension/preeclampsia/eclampsia, cesarean delivery, placental anomalies, and preterm birth. Additionally, infants born to women with a history of endometriosis diagnosis or fibroids were more likely to be low birthweight and have respiratory conditions. Future research should investigate whether pregnant women with a history of endometriosis or fibroids may benefit from targeted screening or intervention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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AJOG at a glance:

Why was the study conducted?

- Prior research has suggested that women with endometriosis and fibroids may be at greater risk of adverse pregnancy outcomes.
- However, much of the research is among a small number of participants and has not investigated differences by infertility history and fertility treatment utilization which may independently increase risk of adverse pregnancy outcomes.

What are the key findings?

- Women with endometriosis or fibroids were at greater risk of hypertensive disorders of pregnancy, cesarean delivery, placental anomalies, and preterm birth.
- Neonates born to non-infertile women with a history of fibroids were more likely to be low birthweight.

What does this study add to what is already known?

- Women with endometriosis or fibroids may have a greater risk of adverse pregnancy outcome which may vary by infertility history and fertility treatment utilization.
- Future research should investigate whether pregnant women with a history of endometriosis or fibroids may benefit from targeted screening or intervention.

Table 1:

Characteristics of deliveries to women aged ≥ 18 in Massachusetts between October 1, 2013 and December 31, 2017

	Total		No history of endometriosis or fibroids diagnosis[1]		History of endometriosis		History of uterine fibroids	
	n	%	n	%	n	%	n	%
Total	91,825	100.0	73,868	100.0	1,560	100.0	4,212	100.0
History of endometriosis	1,560	1.7	-	-	-	-	287	6.8
History of fibroids	4,212	4.6	-	-	287	18.4	-	-
Maternal Age								
Range	18–56		18–56		22–53		21–53	
Mean (SD)	33.12 (4.11)		33.00 (4.03)		34.54 (4.23)		35.78 (4.17)	
18–29	16,135	17.6	13,305	18.0	158	10.1	222	5.3
30–34	43,289	47.1	35,513	48.1	650	41.7	1,438	34.1
35–37	19,546	21.3	15,410	20.9	387	24.8	1,206	28.6
38–40	9,296	10.1	7,138	9.7	233	14.9	807	19.2
> 40	3,559	3.9	2,502	3.4	132	8.5	539	12.8
Race/Ethnicity								
Hispanic	4,258	4.6	3,304	4.5	70	4.5	245	5.8
Non-Hispanic White	69,213	75.4	55,535	75.2	1,234	79.1	2,787	66.2
Non-Hispanic Black	3,085	3.4	2,154	2.9	54	3.5	429	10.2
Non-Hispanic Asian	13,086	14.3	11,145	15.1	168	10.8	644	15.3
Other Non-Hispanic	396	0.4	314	0.4	<11	-	22	0.5
Unknown	1,787	1.9	1,416	1.9	27	1.7	85	2.0
Body Mass Index (BMI; kg/m^2)								
< 22.5	34,902	38.0	28,540	38.6	585	37.5	1,328	31.5
22.5 to < 25.0	20,922	22.8	16,921	22.9	337	21.6	923	21.9
25.0 to < 30.0	20,414	22.2	16,215	22.0	367	23.5	1,081	25.7
30.0+	12,724	13.9	9,866	13.4	236	15.1	746	17.7
Unknown	2,863	3.1	2,326	3.1	35	2.2	134	3.2
Highest level of education								
< HS/HS graduate	2,977	3.2	2,328	3.2	46	2.9	109	2.6
Some college	11,203	12.2	8,569	11.6	191	12.2	489	11.6
College graduate	75,534	82.3	61,319	83.0	1,289	82.6	3,484	82.7
Unknown	2,111	2.3	1,652	2.2	34	2.2	130	3.1
Health Insurance at delivery								
Private	81,700	89.0	65,484	88.7	1,413	90.6	3,815	90.6
Public/Free Care	4,456	4.9	3,702	5.0	64	4.1	150	3.6
Self-pay	5,612	6.1	4,640	6.3	81	5.2	244	5.8
Unknown	57	0.1	42	0.1	<11	-	<11	-
Gravidity[2]								
1	35,639	38.8	29,177	39.5	635	40.7	1,449	34.4

	Total		No history of endometriosis or fibroids diagnosis[1]		History of endometriosis		History of uterine fibroids	
	n	%	n	%	n	%	n	%
2	30,547	33.3	24,647	33.4	491	31.5	1,411	33.5
3–18	25,269	27.5	19,743	26.7	426	27.3	1,333	31.6
Unknown	370	0.4	301	0.4	<11	-	19	0.5
Parity								
1	44,808	48.8	36,040	48.8	885	56.7	2,093	49.7
2	33,952	37.0	27,235	36.9	508	32.6	1,615	38.3
3–15	12,962	14.1	10,506	14.2	166	10.6	502	11.9
Unknown	103	0.1	87	0.1	<11	-	<11	-
Plurality								
Singletons	89,603	97.6	72,177	97.7	1,475	94.6	4,046	96.1
Multiples	2,222	2.4	1,691	2.3	85	5.4	166	3.9
Fertility Group								
ART	7,689	8.4	5,263	7.1	537	34.4	871	20.7
Subfertile/ infertility	13,432	14.6	9,494	12.9	466	29.9	1,112	26.4
Non-infertile	70,704	77.0	59,111	80.0	557	35.7	2,229	52.9
Multiples by fertility group								
ART	993	12.9	687	13.1	69	12.8	109	12.5
Subfertile/ infertile	401	3.0	309	3.3	10	2.1	30	2.7
Non-infertile	828	1.2	695	1.2	<11	1.1	27	1.2
Year of birth								
2013	5,631	6.1	5,172	7.0	22	1.4	125	3.0
2014	22,509	24.5	19,624	26.6	230	14.7	712	16.9
2015	22,178	24.2	17,926	24.3	397	25.4	1,015	24.1
2016	21,441	23.3	16,335	22.1	469	30.1	1,205	28.6
2017	20,066	21.9	14,811	20.1	442	28.3	1,155	27.4

ART=assisted reproductive technologies; HS=high school

1) Gynecological disorders defined as: endometriosis, pelvic pain, and / or uterine fibroids

2) No gravidity data from fetal deaths

Table 2.

Association between history of endometriosis diagnosis prior to delivery and adverse pregnancy outcomes among deliveries to women aged ≥18 in Massachusetts between October 1, 2013-December 31, 2017

	No history of endometriosis		History of endometriosis		Relative Risk (95% Confidence Interval)[1]		
	n	%	n	%	Crude	Adjusted[1]	Adjusted[2]
Total deliveries	90,265	100.0	1,560	100.0			
Maternal outcomes							
Gestational diabetes	7,059	7.8	121	7.8	1.00 (0.84–1.19)	0.90 (0.75–1.07)	0.90 (0.75–1.07)
PIH[3]/Eclampsia/Pre-eclampsia	9,440	10.5	213	13.7	1.30 (1.15–1.48)	1.19 (1.04–1.35)	1.17 (1.03–1.33)
Caesarean delivery[4]	28,677	31.8	680	43.6	1.36 (1.28–1.44)	1.24 (1.18–1.31)	1.22 (1.15–1.29)
Caesarean delivery (primipara only)[4]	13,963	31.8	386	43.6	1.37 (1.27–1.48)	1.21 (1.12–1.30)	1.18 (1.09–1.27)
Placental abnormalities[5]	2,543	2.8	80	5.1	1.83 (1.47–2.27)	1.74 (1.40–2.17)	1.65 (1.33–2.06)
Infant Outcomes							
Total infants	92,429	100.0	1,648	100.0			
Total livebirths	92,178	99.7	1,641	99.6			
Small for gestational age status[6]	6,513	7.2	115	7.2	0.98 (0.81–1.18)	0.95 (0.79–1.14)	0.95 (0.79–1.14)
Low birthweight (<2500 grams)	5,988	6.5	190	11.6	1.36 (1.01–1.83)	1.26 (1.10–1.44)	1.23 (1.07–1.42)
prematurity (<37 weeks)	7,092	7.7	223	13.7	0.95 (0.29–3.14)	1.27 (1.12–1.44)	1.24 (1.09–1.41)
Neonatal prolonged hospital stay[6,7,8]	3,909	4.4	91	6.0	1.30 (1.04–1.63)	1.13 (0.91–1.40)	1.05 (0.86–1.29)
Neonatal Conditions							
Infectious disease[8,9]	856	1.2	15	1.3	1.09 (0.65–1.82)	0.92 (0.55–1.54)	0.89 (0.54–1.48)
Cardiovascular[8,9]	1,573	2.2	42	3.5	1.60 (1.17–2.18)	1.37 (1.01–1.87)	1.28 (0.95–1.73)
Respiratory[8,9]	11,958	16.6	266	22.4	1.32 (1.18–1.48)	1.22 (1.09–1.37)	1.15 (1.04–1.28)
GI/Nutritional[8,9]	4,572	6.3	123	10.4	1.54 (1.23–1.92)	1.21 (1.01–1.44)	1.16 (0.98–1.37)
Neurologic[8,9]	2,902	4.0	61	5.1	1.29 (1.00–1.65)	1.30 (1.01–1.67)	1.26 (0.98–1.62)
Hematologic[8,9]	10,003	13.9	234	19.7	1.43 (1.27–1.62)	1.09 (0.97–1.22)	1.04 (0.93–1.17)

1. Crude and adjusted relative risk approximated using general estimating equations with a log link and Poisson distribution to take into account multiple deliveries by the same women; multivariate models adjusted for maternal age (continuous), body mass index (<25.0, 25.0+, unknown), race (non-Hispanic White, other race/ethnicity, unknown), education (high school + some college, completed college, unknown), plurality (singleton, multiples), and birth year (2013–2017 ordinal categorical variable).

2. Relative risk additionally adjusted for history of hypertension, diabetes, fibroids

3. PIH: Pregnancy Induced Hypertension

4. Excluding those with unknown mode of delivery

5. Placental abnormalities include: ICD 641.0–641.2, 663.5, 667.0, 762.1, O45, P02.1, O43.21, O44, O69

6. Limited to livebirths only

7. Limited analysis to those whose gestational age ≥ 35 weeks, with known data on mode of delivery and birth hospital records. Prolonged stay defined as > 3 days for vaginal delivery or > 5 days for cesarean delivery

8. Relative risk additionally adjusted for gestational age (continuous variable, range 17–44), excluding those with unknown GA.

9. Limited to livebirths October 1, 2013-December 31, 2016 (to allow capture of conditions up to one-year after birth)

Table 3.

Association between history of uterine fibroids prior to delivery and adverse pregnancy outcomes among deliveries to women aged ≥ 18 in Massachusetts between October 1, 2013-December 31, 2017

	No history of uterine fibroids		History of uterine fibroids		Relative Risk (95% Confidence Interval)[1]		
	n	%	n	%	Crude	Adjusted[1]	Adjusted[2]
Total deliveries	87,613	100.0	4,212	100.0			
Maternal morbidity							
Gestational diabetes	6,716	7.7	464	11.0	1.41 (1.29–1.55)	1.06 (0.97–1.16)	1.06 (0.96–1.16)
PIH[3]/Eclampsia/Preeclampsia	9,117	10.4	536	12.7	1.20 (1.11–1.31)	1.12 (1.03–1.21)	1.08 (0.99–1.17)
Caesarean delivery[4]	27,436	31.3	1,921	45.6	1.36 (1.31–1.41)	1.18 (1.14–1.23)	1.17 (1.13–1.21)
Caesarean delivery (primipara only)[4]	13,371	31.3	978	46.7	1.49 (1.42–1.57)	1.22 (1.16–1.28)	1.20 (1.15–1.27)
Placental abnormalities[5]	2,433	2.8	190	4.5	1.63 (1.41–1.88)	1.43 (1.23–1.65)	1.38 (1.19–1.60)
Delivery complications							
Total infants	89,698	100.0	4,379	100.0			
Total livebirths	89,458	99.7	4,361	99.6			
Small for gestational age[6]	6,336	7.2	292	6.9	0.93 (0.82–1.04)	0.97 (0.86–1.09)	0.97 (0.86–1.09)
Low birthweight (<2500 grams)	5,769	6.4	409	9.4	1.03 (0.81–1.32)	1.12 (1.01–1.24)	1.09 (0.98–1.20)
Preterm birth (<37 weeks)	6,802	7.6	513	11.8	1.00 (0.58–1.72)	1.21 (1.11–1.33)	1.17 (1.07–1.29)
Neonatal mortality[6,7,8]	177	0.2	11	0.3	0.72 (0.17–3.09)	1.14 (0.58–2.23)	1.20 (0.61–2.37)
Neonatal prolonged hospital stay[6,8,9]	3,751	4.4	243	5.9	1.33 (1.17–1.53)	1.13 (0.99–1.29)	1.02 (0.90–1.17)
Neonatal Conditions							
Infectious disease[8,10]	817	1.2	54	1.7	1.45 (1.13–1.97)	1.35 (1.01–1.79)	1.23 (0.93–1.61)
Cardiovascular[8,10]	1,498	2.1	117	3.7	1.72 (1.42–2.08)	1.46 (1.20–1.77)	1.29 (1.06–1.55)
Respiratory[8,10]	11,557	16.5	667	20.9	1.26 (1.17–1.36)	1.19 (1.11–1.28)	1.12 (1.04–1.20)
GI/Nutritional[8,10]	4,371	6.2	324	10.2	1.67 (1.48–1.90)	1.30 (1.16–1.46)	1.19 (1.05–1.34)
Neurologic[8,10]	2,827	4.0	136	4.3	1.06 (0.90–1.26)	1.13 (0.95–1.34)	1.07 (0.90–1.27)
Hematologic[8,10]	9,631	13.7	606	19.0	1.41 (1.30–1.52)	1.08 (1.01–1.17)	1.02 (0.95–1.10)

[1] Crude and adjusted relative risk approximated using general estimating equations with a log link and poisson distribution to take into account multiple deliveries by the same women; multivariate models adjusted for maternal age (continuous), body mass index (<25.0, 25.0+, unknown), race (non-Hispanic White, other race/ethnicity, unknown), education (high school + some college, completed college, unknown), plurality (singleton, multiples), and birth year (2013–2017 ordinal categorical variable).

[2] Relative risk additionally adjusted for history of hypertension, diabetes, and endometriosis

[3] PIH: Pregnancy Induced Hypertension

[4] Excluding those with unknown mode of delivery

[5] Placental abnormalities include: ICD 641.0–641.2, 663.5, 667.0, 762.1, O45, P02.1, O43.21, O44, O69

[6] Limited to livebirths only

[7] Neonatal death= 0–27 days after birth

[8] Limited analysis to those whose gestational age ≥ 35 weeks, with known data on mode of delivery and birth hospital records. Prolonged stay defined as > 3 days for vaginal delivery or > 5 days for cesarean delivery

[9] Relative risk additionally adjusted for gestational age (continuous variable, range 17–44), excluding those with unknown GA.

[10] Limited to livebirths October 1, 2013-December 31, 2016 (to allow capture of conditions up to one-year after birth)