Obstetric outcomes in women with pelvic endometriosis: a prospective cohort study

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Objective: To determine whether obstetric outcomes differ between women with endometriosis and those without, where all women undergo first-trimester screening for endometriosis.
Design: A prospective observational cohort study.
Setting: The Early Pregnancy Unit at University College London Hospital, United Kingdom.
Patients: Women with a live pregnancy progressing beyond 12 weeks' gestation and concurrent endometriosis (n = 110) or no endometriosis (n = 393).
Intervention: All women underwent a pelvic ultrasound examination in early pregnancy to examine for the presence of endometriosis and uterine abnormalities.
Main outcome measures: The primary outcome of interest was preterm birth, defined as delivery before 37 completed weeks' gestation. Secondary outcomes included late miscarriage, antepartum hemorrhage, placental site disorders, gestational diabetes, hypertensive disorders of pregnancy, neonates small for gestational age, mode of delivery, intrapartum sepsis, postpartum hemorrhage, and admission to the neonatal unit.
Results: Women with a diagnosis of endometriosis did not have statistically significantly higher odds of preterm delivery (adjusted odds ratio [aOR] 1.85 [95% confidence interval {CI} 0.50–6.90]), but they did have higher odds of postpartum hemorrhage during cesarean section (aOR 3.64 [95% CI 2.07–6.35]) and admission of their newborn infant to the neonatal unit (aOR 3.24 [95% CI 1.08−9.73]). Women with persistent or recurrent deep endometriosis after surgery also had higher odds of placental site disorders (aOR 8.65 [95% CI 1.17–63.71]) and intrapartum sepsis (aOR 3.47 [95% CI 1.02–11.75]).
Conclusion: We observed that women with endometriosis do not have higher odds of preterm delivery, irrespective of their disease subtype. However, they do have higher odds of postpartum hemorrhage during the cesarean section and newborn admission to the neonatal unit. (Fertil Steril® 2024;122:696–705. ©2024 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Endometriosis, pregnancy, preterm delivery, ultrasound

Endometriosis is a common gynecological condition and is estimated to affect between 6% and 10% of women of reproductive age (1). The prevalence of deep and ovarian endometriosis in pregnancy is approximately 5%, which is similar to that of women attending a general gynecology clinic (6%), and approximately 50% of women are unaware that they have this condition (2, 3).

There is no consensus regarding specialist care for women with a diagnosis of endometriosis during pregnancy; however, recent data suggest that endometriosis may increase the risk of adverse obstetric and neonatal outcomes, including preterm birth (4–6). Preterm birth, defined as birth at <37 + 0 weeks of gestation, accounts for 7.4% of all live births in England and Wales. It is the most important single determinant of adverse infant outcomes in terms of both survival and quality of life and is the leading cause of perinatal death and disability (7, 8).

Previous studies reporting on obstetric complications in women with endometriosis are on the basis of fertility populations, retrospective data, or national statistics; the true complication rate in women with endometriosis is unknown (9–14).

Received January 11, 2024; revised May 27, 2024; accepted May 28, 2024; published online June 3, 2024.
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Fertil Steril® Vol. 122, No. 4, October 2024 0015-0282

https://doi.org/10.1016/j.fertnstert.2024.05.162

Recently published international guidance by the European Society of Human Reproduction and Embryology highlights heterogeneous, low-quality data that is unable to guide the clinical care of pregnant women with pelvic endometriosis. There is no evidence to warrant increased antenatal monitoring of pregnant women with endometriosis.

There is an urgent need for high-quality prospective observational data to better define the obstetric risks for women with endometriosis (6). The aim of this study, therefore, was to prospectively evaluate the relationship between pelvic endometriosis and obstetric and neonatal outcomes in pregnant women who underwent screening for endometriosis early in pregnancy.

MATERIALS AND METHODS

This was a single-center, prospective cohort study of women presenting to the Early Pregnancy Unit at University College London Hospital (UCLH) between October 2017 and November 2019. Women were divided into "endometriosis" or "no endometriosis" groups, depending on whether they had a diagnosis of pelvic endometriosis.

Study population

Women with a live pregnancy progressing beyond 12 weeks' gestation who booked for antenatal care at University College London Hospital were included in the study. Women presented either with clinical symptoms of early miscarriage, such as vaginal bleeding or lower abdominal pain, or they attended for reassurance scans because of their history of previous early pregnancy loss. We also included women referred from our antenatal clinics or local family planning services.

All women underwent a systematic, detailed pelvic ultrasound examination, which included an assessment of the location and viability of the pregnancy. Only women who underwent a transvaginal scan were included in the study. The pelvis was examined for the presence of congenital and acquired uterine pathology, including adenomyosis, uterine fibroids, and congenital uterine abnormalities in addition to endometriosis. Diagnoses of major congenital uterine anomalies and adenomyosis were made when there was a historical diagnosis on the basis of previous ultrasound examinations or there was evidence on their ultrasound at the initial visit in pregnancy. Adenomyosis was diagnosed when 1 or more direct signs or several indirect signs, as described by the Morphological Uterus Sonographic Assessment group, were seen (15). Fibroids were diagnosed when there was evidence of well-defined lesions within or connected to the myometrium of the uterine corpus or cervix with posterior shadowing and circumferential vascularity on their initial scan in pregnancy (15, 16). Congenital uterine anomalies were classified according to the revised American Society for Reproductive Medicine classification (17). The adnexa was examined for the presence of ovarian endometriomas and other ovarian and tubal abnormalities. A thorough examination of the anterior and posterior pelvic compartments and the rectosigmoid colon was performed to look for evidence of deep endometriosis. A diagnosis of endometriosis was made when there was a history of previous surgery with histologic confirmation or when there was evidence of lesions on ultrasound, as described by the International Deep Endometriosis Analysis Group (18). All ultrasound examinations were performed by clinicians with advanced skills in noninvasive ultrasound diagnosis of pelvic endometriosis and other gynecological abnormalities. All scans were performed in a standard fashion using a 7.5-Mhz probe (Voluson E8, GE Medical Systems, Milwaukee, WI) as described previously (2). All clinical findings were recorded prospectively in a clinical database that facilitated data entry and retrieval (PIA-Fetal Database, Viewpoint Bildverabeitung GmbH, Wessling, Germany).

We recorded women's demographic data and detailed medical history (age, ethnicity, body mass index [kg/m^2], smoking status, gravidity, and parity). We also recorded a thorough gynecological and obstetric history, including previous diagnosis of endometriosis, cesarean section (CS) delivery, early miscarriage (defined as miscarriage <15 completed weeks of gestation), recurrent miscarriage (defined as 3 or more miscarriages before 15 weeks gestation), late miscarriage (defined as miscarriage between $15 + 0$ and $22 + 6$ weeks gestation), preterm birth, ectopic pregnancy, and pelvic surgery.

Study outcomes

The primary outcome of interest was preterm birth. Secondary outcomes included late miscarriage, antepartum hemorrhage, placental site disorders, gestational diabetes mellitus, hypertensive disorders of pregnancy, neonates small for gestational age (SGA), mode of delivery, intrapartum sepsis, postpartum hemorrhage, and admission to the neonatal unit. Preterm birth was defined as delivery before 37 weeks of gestation. Antepartum hemorrhage was diagnosed when significant bleeding occurred during the antenatal course, requiring admission to the hospital for observation. Placental abruption was diagnosed when placental separation occurred before delivery. Placenta praevia diagnosis was on the basis of ultrasound evidence of the placenta completely or partially covering the internal cervical orifice. Placenta accreta was diagnosed when there was evidence of implantation of the placenta within a previous uterine scar. Gestational diabetes mellitus was diagnosed when there was a positive oral glucose tolerance test. Pregnancy-induced hypertension was defined as persistently raised blood pressure over 140 and 90 mmHg after 20 weeks of gestation. Preeclampsia was diagnosed in the presence of pregnancy-induced hypertension with significant proteinuria. Small for gestational age neonates were identified by birth weight under the 10th centile on customized growth charts. The mode of delivery was categorized as vaginal delivery or CS delivery (emergency or elective). Postpartum hemorrhage was defined as >500 mL of blood loss.

Obstetric and neonatal outcomes were collected from the hospital-based medical records program (EPIC, Epic Systems Corp., Verona, WI) and standardized questionnaires that women were asked to complete and return after their delivery.

Statistical analysis

Statistical analysis was performed using SPSS Statistics version 22.0 (SPSS Inc., Chicago, IL). The distribution of data

was assessed using the Kolmogorov-Smirnov test. Descriptive statistics are presented as mean ± SD for normally distributed data, median (range) for nonnormally distributed data, and n (%) for categorical data. Fischer's exact test was used to compare proportions. A multivariable logistic regression analysis was performed to calculate the adjusted odds ratio (aOR) for adverse outcomes. Any variable that had a coefficient that was significant at the 10% level in the univariable logistic analysis was considered to have a potential confounding effect and was included as a covariate in the multivariable logistic regression analysis. To avoid overestimation of the effect size, only 1 confounding variable was included when 2 possible confounders showed a high correlation, e.g., pregnancy history and concurrent uterine abnormality. Where gravidity and parity were shown to have a similar effect size, only gravidity was used to ensure inclusivity of all previous pregnancies, irrespective of the history of multiple pregnancies, gestation at delivery, or pregnancy loss. For concurrent uterine abnormality, the confounder that demonstrated the greatest effect size was described as most relevant for the outcome and was selected as the confounding variable, i.e., adenomyosis for postpartum hemorrhage.

Details of ethics approval

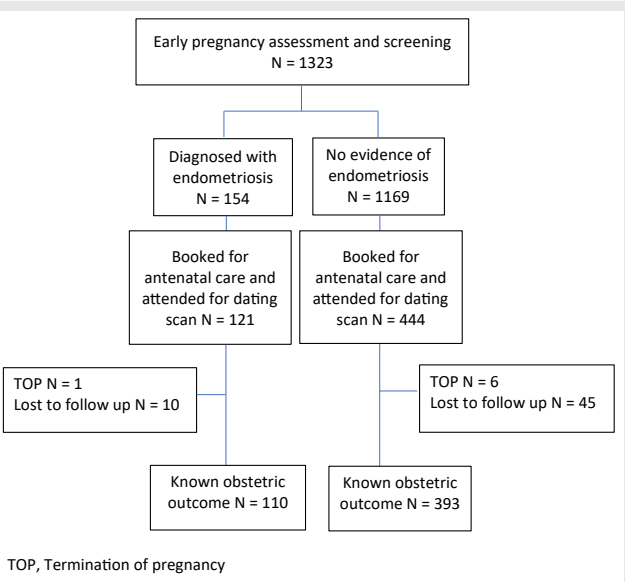
Ethical approval was sought and approved by the West Midlands-Coventry and Warwickshire Research Ethics Committee (date of approval: September 26, 2017, reference: 17/WM/0315). This study was approved by the University College London Hospitals and the University College London Joint Research Office.

RESULTS

Population characteristics

We screened a total of 1,323 women who attended an ultrasound scan during the first trimester of pregnancy. The study population included 503 women who booked antenatal care in our hospital, attended follow-up visits, and whose pregnancies progressed beyond 12 weeks of gestation. Of these 503 women, 21.9% (110/503, 95% confidence interval [CI] 18.3–25.5) had a diagnosis of endometriosis, and 78.1% (393/503, 95% CI 74.5–81.7) did not. For 23.6% (26/110, 95% CI 15.7–31.5) of women with endometriosis, this was a new diagnosis made during their pelvic ultrasound during pregnancy. A total of 22.7% (25/110, 95% CI 14.9–30.5) women had endometriomas alone, 38.2% (42/110, 95% CI 29.1–47.3) women had deep nodules alone, and 30.0% (33/110, 95% CI 21.4–38.6) women had evidence of both endometrioma and deep nodules. The remaining 9.1% (10/110, 95% CI 3.7–14.5) women had a background of surgical excision of endometriosis with no evidence of residual or recurrent endometriosis on their initial pregnancy scan. A patient flowchart showing the inclusion of study participants is presented in Figure 1. Demographic data are shown in Table 1, and primary indications for the first visit are presented in Supplemental Table 1 (available online).

FIGURE 1



Flowchart showing the inclusion of study participants (n = 503).

Bean. Obstetric outcomes: endometriosis. Fertil Steril 2024.

Women with endometriosis were older, more likely to be nulliparous, to have conceived after in vitro fertilization treatments, and were more likely to have undergone pelvic surgery than those in the group without a diagnosis of endometriosis. The groups had similar BMI, smoking status, and ethnicity. There was no statistically significant difference in the rate of multiple pregnancies within the groups, nor were there statistically significant differences in the proportions of women who reported a history of previous recurrent pregnancy loss, ectopic pregnancy, late miscarriage, preterm delivery, or CS delivery.

Concomitant uterine abnormality

A list of concomitant uterine abnormalities according to the presence of endometriosis is shown in Supplemental Table 2. The frequency of a concomitant uterine abnormality was statistically significantly higher in the women with endometriosis than in the group without a diagnosis of endometriosis (27.3% [30/110] vs. 13.5% [53/393]; $P=.001$). Women with active deep endometriotic lesions on pelvic ultrasound had a higher risk of having a concomitant uterine abnormality, with an odds ratio (OR) of 4.11 (95% CI 1.31–12.91) than those without evidence of active deep disease. All women with endometriosis who had evidence of a concurrent congenital uterine anomaly also had evidence of active deep disease. All women with a diagnosis of adenomyosis were diagnosed before their pregnancy. A total of 78% (7/9, 95% CI 50.9–100.0) of women with a major congenital uterine anomaly were diagnosed before pregnancy. Neither of the 2

TABLE 1

Demographic and clinical characteristics of 110 women with endometriosis and 393 women without a diagnosis of endometriosis (n = 503).

Characteristic	Endometriosis (n = 110)	No endometriosis (n = 393)
Age (y)	34 (22–44)	32 (16–49)
BMI (kg/m^2)	23.7 (16.6–42.2)	23.9 (15.8–54.8)
Smoking status	5 (4.5)	27 (6.9)
Self-reported ethnicity, n (%)		
Caucasian	73 (66.4)	232 (59.0)
Afro-Caribbean	10 (9.1)	50 (12.7)
South Asian	15 (13.6)	51 (13.0)
East Asian	5 (4.5)	16 (4.1)
Mixed/Other	7 (6.4)	44 (11.2)
Parity, n (%)		
0	77 (70.0)	211 (53.7)
1	27 (24.5)	118 (30.0)
≥2	6 (5.5)	64 (16.3)
Gravidity, n (%)		
1	52 (47.3)	126 (32.1)
2	30 (27.3)	121 (30.8)
≥3	28 (25.5)	146 (37.2)
ART treatment-induced conception	29 (26.4)	25 (6.4)
Multiple pregnancies	8 (7.3)	17 (4.3)
Gynecological history, n (%)		
Early miscarriage	36 (32.7)	179 (45.5)
Recurrent miscarriage	7 (6.4)	12 (3.1)
Ectopic pregnancy	4 (3.6)	22 (5.6)
Pelvic surgery	36 (32.7)	27 (6.9)
Obstetric history, n (%)		
Previous late miscarriage	0 (0.0)	10 (2.5)
Previous preterm delivery	1 (0.9)	16 (4.1)
Previous CS	15 (13.6)	58 (14.8)

Note: Data are given as median (range) or n (%).
Early miscarriage is defined as <15 + 0 weeks gestation.
Recurrent miscarriage is defined as ≥3 miscarriages.
ART = assisted reproductive technology; BMI = body mass index; CS = cesarean section.

Bean. Obstetric outcomes: endometriosis. Fertil Steril 2024.

women diagnosed in early pregnancy had evidence of concurrent pelvic endometriosis.

Risk of adverse obstetric and neonatal outcomes

The median gestation at delivery was 39 + 1 (range 32 + 4–42 + 1) weeks in the endometriosis group and 39 + 4 (range 24 + 3–42 + 1) weeks in the group without a diagnosis of endometriosis (P=.010). There was a higher proportion of women in the endometriosis group that experienced preterm birth than in the group without a diagnosis of endometriosis, but this was not statistically significant on univariate analysis or when adjustments were made for covariates, including age, conception after assisted reproductive technology treatment, and concurrent presence of uterine adenomyosis. There were no cases of extremely preterm birth <32 weeks of gestation in the endometriosis group. However, infants born to women with endometriosis were more likely to require admission to the neonatal unit, irrespective of the mode of delivery (aOR 3.24, 95% CI 1.08–9.73) (Table 2).

There were no statistically significant differences in the proportions of women in the endometriosis group and the group without a diagnosis of endometriosis who experienced a late miscarriage (15 + 0 to 23 + 6 weeks gestation), placenta praevia, placenta accreta, significant antepartum hemorrhage, gestational diabetes mellitus, intrapartum sepsis, or SGA neonates. A greater proportion of women with endometriosis were diagnosed with hypertensive disorders of pregnancy, but this was not statistically significant in multivariate analysis.

More than half of women with endometriosis were delivered via CS, but there was no evidence of higher odds when adjustments were made for covariates. Women with endometriosis were more likely to experience a postpartum hemorrhage during CS, irrespective of their age, gravidity, mode of conception, history of previous pelvic surgery, and concurrent presence of uterine adenomyosis (aOR 3.64, 95% CI 2.07–6.35). The indications for CS delivery were similar for those with endometriosis and for the group without a diagnosis of endometriosis (Supplemental Table 3).

Intrapartum and postpartum complications are presented in Supplemental Table 4. There were no cases of cesarean hysterectomy, bowel injury, or bladder injury in the study population. There were 2 cases of stillbirth and 1 neonatal death in the group without a diagnosis of endometriosis, but none in the endometriosis group.

TABLE 2

Obstetric and neonatal outcomes of 110 women with endometriosis and 393 women without a diagnosis of endometriosis (n = 503).

Outcome	Endometriosis (n = 110), n/N (%)	No endometriosis (n = 393), n/N (%)	P[a]	OR (95% CI)	aOR (95% CI)
PTB (23 + 0–36 + 6 wks)	13/109 (11.9)	25/391 (6.4)	.065	1.98 (0.98–4.02)	[b]1.85 (0.50–6.90)
Late miscarriage (15+1–22+6 wks)	1/110 (0.9)	2/393 (0.5)	>.999	1.79 (0.16–19.67)	
Placenta preavia/accreta	3/109 (2.8)	3/391 (0.8)	.121	3.66 (0.73–18.40)	
Placenta praevia	2/109 (1.8)	3/391 (0.8)	.590	2.42 (0.40–14.65)	
Placenta accreta	1/109 (0.9)	0/391 (0.0)	.218	—	
APH/abruption	2/109 (1.8)	7/391 (1.8)	>.999	1.03 (0.21–5.01)	
Hypertensive disorders of pregnancy	8/109 (7.3)	11/391 (2.8)	**.011**	**3.79 (1.39–10.35)**	[c]3.08 (0.99–9.62)
PIH	7/109 (6.4)	8/391 (2.0)	**.026**	**3.29 (1.16–9.27)**	[c]2.32 (0.69–7.74)
PET	4/109 (3.7)	6/391 (1.5)	.236	2.44 (0.68–8.82)	
GDM	10/109 (9.2)	35/391 (9.0)	>.999	1.03 (0.49–2.15)	
Intrapartum sepsis	7/109 (6.4)	17/391 (4.3)	.445	1.51 (0.61–3.74)	
NNU admission	14/109 (12.8)	25/389 (6.4)	**.041**	**2.16 (1.08–4.31)**	[d]**3.24 (1.08–9.73)**
SGA	6/109 (5.5)	41/391 (10.5)	.138	0.50 (0.21–1.20)	
CS	56/109 (51.4)	145/391 (37.1)	**.008**	**1.79 (1.17–2.75)**	[c]1.26 (0.78–2.04)
Emergency CS	33/109 (30.3)	82/391 (21.0)	**.053**	**1.64 (1.02–2.63)**	[c]1.46 (0.86–2.47)
Elective CS	23/109 (21.1)	63/391 (16.1)	.251	1.39 (0.82–2.37)	
PPH	57/109 (52.3)	117/391 (29.9)	**<.001**	**2.57 (1.66–3.96)**	[c]**2.44 (1.50–3.97)**
Vaginal delivery	17/109 (15.6)	70/391 (17.9)	.699	0.85 (0.48–1.51)	
CS	40/109 (36.7)	47/391 (12.0)	**<.001**	**4.24 (2.59–6.96)**	[c]**3.64 (2.07–6.35)**

Note: Data are given as n/N (%). Bold indicates significance level $P < .5$.
aOR = adjusted odds ratio; APH = antepartum hemorrhage; ART = assisted reproductive technology; CI = confidence interval; CS = cesarean section; GDM = gestational diabetes mellitus; NNU = neonatal unit; OR = odds ratio; PET = preeclampsia; PIH = pregnancy-induced hypertension; PPH = postpartum hemorrhage >500 mL; PTB = preterm birth; SGA = small for gestational age neonate.
[a] Fisher's exact test.
[b] aOR adjusted for age, ART conception, and concurrent presence of uterine adenomyosis.
[c] aOR adjusted for age, gravidity, ART conception, history of early miscarriage, previous pelvic surgery, and concurrent presence of uterine adenomyosis.
[d] Adjusted for cesarean section delivery.

Bean. Obstetric outcomes: endometriosis. Fertil Steril 2024.

Risk of adverse obstetric and neonatal outcomes in women with different disease subtypes

The proportion of women who experienced preterm delivery, antepartum hemorrhage, hypertensive disorders of pregnancy, CS delivery, postpartum hemorrhage, and neonatal unit admission was similar in women with evidence of deep disease and those without (Supplemental Table 5). There were no cases of late miscarriage, placenta praevia, placenta accreta, or SGA neonates in the group of women without deep disease. There were no statistically significant differences in outcomes between women who had a surgical diagnosis and those who had an ultrasound diagnosis of endometriosis (Supplemental Table 6).

To understand whether surgery for deep endometriosis has an impact on pregnancy outcomes, we performed a further analysis in a subgroup of women who had residual or recurrent deep endometriosis after previous excision surgery. This subgroup of women had statistically significantly higher odds of placenta praevia (aOR 8.65, 95% CI 1.17–63.71), intrapartum sepsis (aOR 3.47, 95% CI 1.02–11.75), neonatal unit admission (aOR 3.24, 95% CI 1.08–9.73) and postpartum hemorrhage (aOR 6.20, 95% CI 1.55–24.89) than women without a diagnosis of endometriosis (Table 3).

DISCUSSION

Principal findings of this study

Our study showed that most women with endometriosis do not have statistically significantly higher odds of preterm delivery, irrespective of their disease subtype. Women with endometriosis do appear to have higher odds of excessive bleeding during CSs, and their newborn infants are more likely to be admitted to the neonatal unit. Women with residual or recurrent deep disease who have had previous surgery may have higher odds of adverse outcomes, including placental site disorders and intrapartum sepsis.

Strengths and limitations

This is the first prospective observational study evaluating obstetric and neonatal outcomes for women with endometriosis, where all women in the study underwent screening for the presence and subtype of endometriosis. The study had a consistent methodology, and we were able to control for the mode of conception and the presence of concurrent uterine abnormalities, which may have an independent impact on the outcomes of interest. All scans were performed by expert operators and were conducted at a center that has reported previously 94% diagnostic accuracy for

TABLE 3

Obstetric and neonatal outcomes in 24 women with residual or recurrent deep endometriosis (DE) and 393 women without a diagnosis of endometriosis.

Outcome	No endometriosis (n = 393) n/N (%)	Residual or recurrent DE (n = 24) n/N (%)	P[a]	OR (95% CI)	aOR (95% CI)
PTB (23 + 0–36 + 6 wks), n/N (%)	25/391 (6.4)	4/23 (17.4)	.068	3.08 (0.97–9.75)	[b]1.86 (0.50–6.90)
Late miscarriage (15 + 1–22 + 6 wks)	2/393 (0.5)	1/24 (4.2)	.163	8.50 (0.74–97.23)	[b]7.33 (0.28–194.29)
Placenta praevia/accreta	3/391 (0.8)	3/23 (13.0)	**.003**	**19.40 (3.68–102.26)**	[b]**8.65 (1.17–63.71)**
APH/abruption	7/391 (1.8)	1/23 (4.4)	.370	2.49 (0.29–21.17)	
Hypertensive disorders of pregnancy	11/391 (2.8)	2/23 (8.7)	.101	4.56 (0.91–22.82)	[c]1.30 (0.09–19.3)
GDM	25/391 (9.0)	2/23 (8.7)	>.999	0.97 (0.21–4.30)	
Intrapartum sepsis	17/391 (4.3)	4/23 (17.4)	**.023**	**4.63 (1.42–15.11)**	[d]**3.47 (1.02–11.75)**
NNU admission	25/389 (6.4)	5/23 (21.7)	**.019**	**4.07 (1.39–11.86)**	[d]**3.24 (1.08–9.73)**
SGA	41/391 (10.5)	2/23 (8.7)	>.999	0.81 (0.18–3.59)	
CS delivery	145/391 (37.1)	14/23 (60.9)	**.028**	**2.64 (1.11–6.25)**	[c]1.48 (0.44–5.04)
PPH	117/391 (29.9)	14/23 (60.9)	**.003**	**3.64 (1.53–8.65)**	[c]**6.20 (1.55–24.89)**

Note: Data are given as n/N (%). Bold indicates significance level $P < .5$.
aOR = adjusted odds ratio; APH = antepartum hemorrhage; ART = assisted reproductive technology; CI = confidence interval; CS = cesarean section; GDM = gestational diabetes mellitus; NNU = neonatal unit; OR = odds ratio; PPH = postpartum hemorrhage >500 mL; PTB = preterm birth; SGA = small for gestational age neonate.
[a] Fisher's exact test.
[b] aOR adjusted for age, ART treatment-induced conception, and concurrent presence of uterine adenomyosis.
[c] aOR adjusted for age, gravidity, ART treatment-induced conception, history of early miscarriage, previous pelvic surgery, and concurrent presence of uterine adenomyosis.
[d] Adjusted for cesarean section delivery.

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ultrasound diagnosis of deep endometriosis, limiting the risk of selection bias (19).

Surgery and histology remain the gold-standard diagnostic techniques internationally. Most patients in the endometriosis group had a prepregnancy-related diagnosis of endometriosis, which is an advantage of this study. We acknowledge that those women in the endometriosis group who were diagnosed on ultrasound alone have not had surgical confirmation of endometriosis, and there may be falsely identified cases of endometriosis on ultrasound. Some may consider the lack of surgical confirmation of endometriosis in all patients to be a limitation of our study. However, laparoscopy is no longer considered a diagnostic reference standard for endometriosis and is now only recommended in women with persistent symptoms and negative imaging results or where empirical treatment has been unsuccessful (6). We acknowledge that we may have failed to detect endometriosis in some women in the group without a diagnosis of endometriosis, particularly those women with peritoneal disease. Peritoneal endometriosis is common, not always detectable on pelvic ultrasound, and may be found incidentally at laparoscopy (20). Only including women with a surgical diagnosis would have provided a more robust method of screening and description of disease subtypes. However, women with endometriosis are increasingly being managed conservatively, and only including those with a surgical diagnosis would have limited the population studied to only those women with symptomatic disease or those who opted for surgery. Women with surgical confirmation of endometriosis had a higher incidence of preterm birth, placental site disorders, antepartum hemorrhage, CS, and neonatal unit admission. Failure to reach statistical significance in our study may be because of small sample sizes in both groups. Because the group without a diagnosis of endometriosis is likely to include some women with mild and minimal endometriosis, the findings of our study should be interpreted with caution in relation to women with mild and minimal diseases.

A further limitation of this study is that we included only live pregnancies that progressed beyond 12 weeks of gestation, excluding pregnancy losses in the first trimester. This could result in potential live birth bias and exaggeration of the associations reported. In addition, several of the secondary outcomes of interest for obstetric and neonatal risks are uncommon. We acknowledge that the limited sample size in our study population may lead to nonstatistically significant associations, and therefore large study populations or meta-analyses are required to provide meaningful results and clarify potential risks.

Logistic regression analysis was chosen as the statistical model for all outcomes in this study, as the primary outcome of interest, preterm birth, has a low prevalence. The OR for secondary outcomes that have a high prevalence in the study population, specifically CS delivery and postpartum hemorrhage, may be overestimated using logistic regression analysis and should be interpreted with this in mind.

Interpretation of results

Meta-analyses performed by Lalani et al. (21) in 2018, Zullo et al. (22) in 2017, and Breintoft et al. (23) in 2021 demonstrated higher odds of preterm birth in women with a diagnosis of pelvic endometriosis (OR 1.63, 95% CI 1.32–2.01, OR 1.70, 95% CI 1.40–2.06, and OR 1.46, 95% CI 1.26–1.69, respectively). The 24 studies included by Zullo et al. (22) in 2017; 23 studies included by Lalani et al. (21) in 2018; and 39 studies included by Brentoft et al. (23) in 2021 were heterogeneous in their methodology and diagnostic criteria, with the mode of conception and presence of concurrent uterine

abnormalities not consistently considered. Proposed mechanisms for the association between endometriosis and preterm birth include higher levels of pro-inflammatory mediators (prostaglandin E2, cyclooxygenase-2, and interleukin-8) in the peritoneal fluid of women with endometriosis, causing uterine muscle contraction and cervical ripening, and progesterone resistance of the endometrium interfering with placentation (24, 25). Our study reported an OR of similar magnitude to previous literature and suggests there may be an association between endometriosis and preterm birth. However, our results did not reach the threshold of significance on multivariable analysis, where the mode of conception and the presence of concurrent uterine abnormalities were considered. We did not demonstrate a significant association when considering the subtype of endometriosis, previous surgical excision, or mode of diagnosis. Exacoustos et al. (26) in 2016 demonstrated the strongest association between the presence of endometriosis and preterm birth, with an OR of 6.87 (95% CI 3.07–15.36) for women with persistent rectovaginal endometriosis after surgery. Farella et al. (27) in 2020 also demonstrated a higher prevalence of preterm birth in women with a history of surgical management of endometriosis, especially in those with a deep disease of the rectum or bladder, but their results may have been affected by a high incidence of assisted reproductive technology treatment-induced conception within their population. In our subgroup analysis of women with residual or recurrent disease, we did not observe higher odds of preterm delivery. Glavind et al. (28) in 2017 reported increased odds of preterm delivery, irrespective of the mode of conception, with the risk being highest for very preterm birth (aOR 1.91, 95% CI 1.16–3.15).

This study demonstrates higher odds of postpartum hemorrhage for women with endometriosis who were delivered via CS. Our findings are in agreement with Saraswat et al. (10) (2017), Yi et al. (29) (2020), and Velez et al. (30) (2022), who reported an increased risk of postpartum hemorrhage with a diagnosis of endometriosis, but differ from the meta-analyses published by Horton et al. (31) (2019), Lalani et al. (21) (2018), and Breintoft et al. (23) (2021), who found that endometriosis was not associated with postpartum hemorrhage. Theories that may support excessive blood loss at the CS section include angiogenesis, a possible association with mild bleeding disorders, pelvic adhesions, surgical complexity, increased operating time, or bleeding from endometriotic deposits (32, 33). Decidualization of endometriotic lesions is a hormonally induced phenomenon that occurs in approximately one-third of women with endometriosis during pregnancy (2). Stromal vascularity, an influx of immune cells, and edema from lesions may also contribute to intraoperative blood loss (34–36). Some women who experience excessive intraperitoneal bleeding at ovulation are at increased risk of developing deep endometriosis, but should a bleeding disorder be of clinical importance, we would also expect excess blood loss during vaginal delivery (37). Endometriotic lesions may be more prone to bleeding in pregnancy and when disturbed during surgery (33). Women with anterior compartment disease, excessive exploration of the posterior pelvic compartment, or exteriorization of the uterus through the abdominal incision at CS could be most at risk. Intrapartum sepsis is commonly acknowledged as a risk factor for postpartum hemorrhage, and although we demonstrated higher odds of postpartum hemorrhage in women with endometriosis compared with those without, higher odds of intrapartum sepsis were only identified in those with persistent deep endometriosis after surgery. This is in keeping with data published by Lafleur et al. (38) (2022) in a cohort of women with active endometriosis in pregnancy after previous surgery.

Our study showed higher odds of newborn admission to the neonatal unit for infants born to mothers with a diagnosis of endometriosis (OR 3.24, 95% CI 1.08–9.73). There was no evidence that women with endometriosis had higher odds of having an SGA infant. These findings are in agreement with Horton et al. (31) (2019), who also reported higher odds of neonatal unit admission for women with endometriosis (OR 1.29, 95% CI 1.07–1.55; 5 studies), but no increased risk of SGA.

On univariate analysis, our study showed that women with endometriosis had higher odds of CS delivery. The odds of CS delivery were similar to those presented in existing published literature (OR 1.86, 95% CI 1.51–2.29; 20 studies) (21). Leone Roberti Maggiore et al. (39) suspected that previous surgical intervention may be a contributing factor to the increased risk of CS delivery in women with endometriosis. In multivariate analysis, which included adjustment for previous pelvic surgery, the association was no longer statistically significant.

Multiple previous studies have highlighted an association between endometriosis and placenta praevia (OR 1.67–61.56) (21, 23, 26, 29–31, 39). In our study, we did not corroborate these findings but were able to demonstrate this in the subgroup of women with recurrent or residual deep disease after surgical excision of endometriosis (OR 8.65, 95% CI 1.17–63.71). Kunz et al. (40) (2000) suggested a possible explanation for abnormal uterine contractions observed in women with endometriosis, leading to abnormal blastocyst implantation.

We did not demonstrate any statistically significant association between the presence of endometriosis and antepartum hemorrhage, placental abruption, gestational diabetes, or hypertensive disorders of pregnancy. This is in keeping with previous studies (5, 31, 39).

Lalani et al. (21) (2018) described the association of endometriosis with stillbirth (OR 1.29, 95% CI 1.10–1.52; 7 studies) and neonatal death (OR 1.78, 95% CI 1.46–2.16) as concerning, warranting further study. Breintoft et al. (23) (2021) also demonstrated increased odds of stillbirth (OR 1.27, 95% CI 1.07–1.51). Although our study detected no association, both outcomes are uncommon, affecting $<1\%$ of pregnancies, and therefore it is unlikely that we would have been able to detect a difference (41). Although the proportion of women who had experienced a previous early miscarriage <15 weeks of gestation was higher in the group without a diagnosis of endometriosis, this study was not designed to assess this outcome, which is likely confounded by differences in gravidity between the 2 groups.

Several case reports describe uterine rupture, spontaneous hemoperitoneum, uroperitoneum, and bowel

perforation in women with endometriosis during pregnancy (42–47). None of these complications were observed in our study population.

CONCLUSIONS

This study did not identify endometriosis as a statistically significant risk factor for preterm delivery and supports the European Society of Human Reproduction and Embryology guidance that women with endometriosis do not warrant increased antenatal care. There is no evidence to support routine screening of women for the presence of endometriosis preconceptually or in early pregnancy.

Acknowledgments

The authors thank all the women who attended the Early Pregnancy Unit at University College London Hospital and participated in this study.

CRediT Authorship Contribution Statement

Elisabeth M.R. Bean: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Jure Knez:** Writing – review & editing, Methodology. **Nikolaos Thanatsis:** Data curation. **Lucrezia De Braud:** Data curation. **Fatima Taki:** Data curation. **Martin Hirsch:** Writing – review & editing. **Anna David:** Writing – review & editing, Methodology. **Davor Jurkovic:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Conceptualization.

Declaration of Interests

E.M.R.B. reported serving as a senior council member of the British Society of Gynaecological Endoscopy. J.K. reported receiving lecture fees from The Slovenian Medical Association and serving as the vice president of the Slovene Association of Gynaecologists and Obstetricians. N.T. has nothing to disclose. L.D.B. has nothing to disclose. F.T. has nothing to disclose. M.H. reported serving as a senior council member of the British Society of Gynaecological Endoscopy and receiving consulting fees to their institution and funding for attendance at the World Endometriosis Congress from Theramex in relation to fibroid management. A.D. has nothing to disclose. D.J. has nothing to disclose.

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Resultados obstétricos en mujeres con endometriosis pélvica: un estudio prospectivo de cohortes

Objetivo: Determinar si los resultados obstétricos entre las mujeres con endometriosis y las que no la tienen difieren, donde todas las mujeres se han sometido a pruebas de detección de endometriosis en el primer trimestre.

Diseño: Un estudio prospectivo observacional de cohortes.

Lugar: The Early Pregnancy Unit at University College London Hospital, Reino Unido.

Pacientes(s): Mujeres con un embarazo que progresa más allá de las 12 semanas de gestación y endometriosis concurrente COINCIDENTE (n = 110) o sin endometriosis (n = 393).

Intervención(es): Todas las mujeres se sometieron a una ecografía pélvica al principio del embarazo para detectar la presencia de endometriosis y anomalías ANORMALIDADES uterinas.

Principal(es) medida(s) de resultado(s): El resultado primario de interés fue el parto prematuro, definido como el parto antes de las 37 semanas completas de gestación. Los resultados secundarios incluyeron aborto espontáneo tardío, hemorragia antes del parto, trastornos del sitio placentario, diabetes gestacional y trastornos hipertensivos del embarazo, recién nacidos pequeños para la edad gestacional, modo TIPO de parto, sepsis intraparto, hemorragia posparto e ingreso a la unidad neonatal.

Resultado(s): Las mujeres con un diagnóstico de endometriosis no tuvieron probabilidades significativamente mayores de parto prematuro (odds ratio ajustado [aOR] 1.85 [intervalo de confianza {CI} del 95%: 0.50–6.90]), pero sí tuvieron mayores probabilidades de hemorragia posparto durante la cesárea (aOR 3.64 [CI 95% 2.07–6.35]) e ingreso de su recién nacido a la unidad DE CUIDADOS neonatalES (aOR 3.24 [CI 95% 1.08–9.73]). Las mujeres con endometriosis profunda persistente o recurrente después de la cirugía también tuvieron mayores probabilidades de sufrir trastornos del sitio DE INSERCIÓN placentariA (aOR 8.65 [CI 95% 1.17–63.71]) y sepsis intraparto (aOR 3.47 [CI 95% 1.02–11.75]).

Conclusión(es): Observamos que las mujeres con endometriosis no tienen mayores probabilidades de parto prematuro, independientemente del subtipo de su enfermedad. Sin embargo, sí tienen mayores probabilidades de sufrir hemorragia posparto durante la cesárea y el ingreso del recién nacido en la unidad neonatal.