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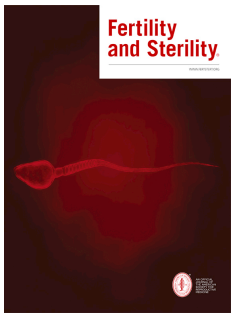

Obstetric outcomes in women with pelvic endometriosis: A prospective cohort study

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TITLE PAGE

Running title: Obstetric outcomes: women with endometriosis

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Capsule: Women with endometriosis did not have higher odds of preterm delivery, but did have higher odds of haemorrhage during Caesearaen section and newborn admission to the neonatal unit.

Abstract

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

Subjects

Women with a live pregnancy progressing beyond 12 weeks' gestation and concurrent endometriosis (n=110) or no endometriosis (n=393)**.**

Exposure

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 haemorrhage, placental site disorders, gestational diabetes, hypertensive disorders of

pregnancy, neonate small for gestational age, mode of delivery, intrapartum sepsis, postpartum haemorrhage and admission to the neonatal unit.

Results

Women with a diagnosis of endometriosis did not have statistically significantly higher odds of preterm delivery (aOR 1.85 (95% CI 0.50-6.90)), but they did have higher odds of postpartum haemorrhage during Caesarean section (aOR 3.64 (95% CI 2.07-6.35);) and admission of their newborn baby 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 haemorrhage during Caearean section and newborn admission to the neonatal unit.

Funding

None

Keywords

Endometriosis, Pregnancy, Preterm delivery, Ultrasound

Introduction

Endometriosis is a common gynaecological condition and estimated to affect between 6-10% 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 gynaecology 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 suggests that endometriosis may increase the risk of adverse obstetric and neonatal outcomes, including preterm birth (4-6). Preterm birth, defined as birth at less than 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 outcome 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 based on fertility populations, retrospective data or national statistics, the true complication rate in women with endometriosis is unknown(9-14).

Recently published international guidance by the European Society of Human Reproduction and Embryology (ESHRE) highlights heterogenous 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-centre, 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 UCLH 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 from 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 based on previous ultrasound examinations or there was evidence on their ultrasound at the initial visit in pregnancy. Adenomyosis was diagnosed when one 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 were 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 carried out to look for evidence of deep endometriosis. A diagnosis of endometriosis was made when there was a history of previous surgery with histological confirmation or if there was evidence of lesions on ultrasound, as described by the International Deep Endometriosis Analysis Group(18). All ultrasound examinations were carried out by clinicians with advanced skills in non-invasive ultrasound diagnosis of pelvic endometriosis and other gynaecological abnormalities. All scans were performed in a standard fashion using a 7.5-Mhz probe (Voluson E8, GE Medical Systems, Milwaukee, WI, USA) as previously described(2). All clinical findings were recorded prospectively in a clinical database which facilitated data entry and retrieval (PIA-Fetal Database, Viewpoint Bildverabeitung GmbH, Wessling, Germany).

We recorded women's demographic data and a detailed medical history (age, ethnicity, body mass index (kg/m^2), smoking status, gravidity and parity). We also recorded a thorough gynaecological and obstetric history, including previous diagnosis of endometriosis, Caesarean section delivery, early miscarriage (defined as miscarriage <15 completed weeks' gestation), recurrent miscarriage (defined as three or more miscarriages before 15 weeks' gestation), late miscarriage (defined as miscarriage between 15+0 to 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 haemorrhage, placental site disorders, gestational diabetes mellitus, hypertensive disorders of pregnancy , neonate small for gestational age, mode of delivery, intrapartum sepsis, postpartum haemorrhage and admission to the neonatal unit. Preterm birth was defined as delivery before 37 completed weeks' gestation. Antepartum haemorrhage was diagnosed when significant bleeding occurred during the antenatal course, requiring admission to hospital for observation. Placental abruption was diagnosed when placental separation occurred before delivery. Placenta praevia diagnosis was based on ultrasound evidence of the placenta completely or partially covering the internal cervical os. 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 140/90mmHg after 20 weeks' gestation. Pre-eclampsia (PET) was diagnosed in the presence of pregnancy induced hypertension with significant proteinuria. Small for gestational age neonates were identified by birth weight

188 under the 10th centile on customised growth charts. Mode of delivery was categorised into
189 vaginal delivery or Caesarean section delivery (emergency or elective). Postpartum
190 haemorrhage was defined as more than 500ml of blood loss.
191
192 Obstetric and neonatal outcomes were collected from the hospital based medical records
193 programme (EPIC, Epic Systems Corp., Verona, WI, USA) and standardised questionnaires
194 that women were asked to complete and return following their delivery.

195 Statistical Analysis

196 Statistical analysis was performed using SPSS Statistics version 22.0 (IBM Corp.). The
197 distribution of data was assessed using the Kolmogorov-Smirnov test. Descriptive statistics
198 are presented as mean +- SD for normally distributed data, median (range) for non-normally
199 distributed data and n (%) for categorical data. The Fischer's exact test was used to compare
200 proportions. Multivariable logistic regression analysis was performed to calculated adjusted
201 odds ratio (aOR) for adverse outcomes. Any variable that had a coefficient that was
202 significant at the 10% level in the univariable logistic analysis was considered to have a
203 potential confounding effect and was included as a covariate in the multivariable logistic
204 regression analysis. To avoid overestimation of the effect size, only one confounding
205 variable was included when two possible confounders showed a high correlation e.g.
206 pregnancy history and concurrent uterine abnormality. Where gravidity and parity were
207 shown to have a similar effect size, only gravidity was used to ensure inclusivity of all
208 previous pregnancies, irrespective of the history of multiple pregnancy, gestation at delivery
209 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 haemorrhage.

Details of ethics approval

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

Results

Population characteristics

We screened a total of 1323 women who attended for an ultrasound scan during the first trimester of pregnancy. The study population included 503 women who booked for antenatal care in our hospital, attended for follow up visits and in whom the pregnancy progressed beyond 12 weeks' gestation. Of these 503 women, 110/503 (21.9%, 95% CI 18.3–25.5) had a diagnosis of endometriosis and 393/503 (78.1%, 95% CI 74.5–81.7) women did not. For 26/110 (23.6%, 95% CI 15.7–31.5) women with endometriosis, this was a new diagnosis made during their pelvic ultrasound in pregnancy. 25/110 (22.7%, 95% CI 14.9-30.5) women had endometriomas alone, 42/110 (38.2%, 95% CI 29.1–47.3) women had deep nodules alone and 33/110 (30.0%, 95% CI 21.4–38.6) women had evidence of both endometrioma and deep nodules. The remaining 10/110 (9.1%, 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 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.

Women with endometriosis were older, more likely to be nulliparous, to have conceived following in vitro fertilization techniques 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 pregnancy within the groups, nor were there statistically significant differences in the proportions who reported a history of previous recurrent pregnancy loss, ectopic pregnancy, late miscarriage, preterm delivery or Caesarean section 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 (30/110(27.3%) vs 53/393(13.5%); P=0.001). Women with active deep endometriotic lesions on pelvic ultrasound had a higher risk of having a concomitant uterine abnormality, with an 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 prior to their pregnancy. 7/9 (78%, 50.9-100.0) women with a major congenital uterine anomaly were diagnosed prior to

pregnancy. Neither of the two 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 weeks (range 32+4 to 42+1) in the endometriosis group and 39+4 weeks (range 24+3 to 42+1) in the group without a diagnosis of endometriosis (P=0.010). There were 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 following assisted reproductive technology and concurrent presence of uterine adenomyosis. There were no cases of extreme preterm birth <32 weeks' gestation in the endometriosis group. However, babies 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 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 haemorrhage, gestational diabetes mellitus, intrapartum sepsis or small for gestational age neonates. A greater proportion of women with endometriosis were diagnosed with hypertensive disorders of pregnancy, but this was not statistically significant on multivariate analysis.

More than half of women with endometriosis were delivered by Caesarean section but there was no evidence of higher odds when adjustments were made for covariates. Women with endometriosis were more likely to experience a postpartum haemorrhage during Caesarean section, 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 Caesarean section 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 caesarean hysterectomy, bowel injury or bladder injury in the study population. There were two cases of stillbirth and one neonatal death in the group without a diagnosis of endometriosis, but none in the endometriosis group.

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

The proportion of women who experienced preterm delivery, antepartum haemorrhage, hypertensive disorders of pregnancy, Caesarean section delivery, postpartum haemorrhage 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 small for gestational age 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 that had an ultrasound diagnosis of endometriosis (Supplemental table 6).

In order 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 haemorrhage (aOR 6.20 (95% CI 1.55-24.89)) than women without a diagnosis of endometriosis (Table 3).

Discussions

Principal findings of this study

Our study showed that the majority of women with endometriosis do not have statistically significant higher odds of preterm delivery, irrespective of their disease subtype. Women with endometriosis do appear to have higher odds of excessive bleeding during Caesarean section and their newborn babies 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 consistent methodology and we were able to control for mode of conception and 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 centre which has previously reported on 94% diagnostic accuracy for ultrasound diagnosis of deep endometriosis, limiting the risk of selection bias(19).

Surgery and histology remain the gold standard diagnostic technique internationally . The majority of patients in the endometriosis group had a pre-pregnancy 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 as a limitation of our study. However, laparoscopy is no longer considered 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 subtype. 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 that opted for surgery. Women with surgical confirmation of endometriosis had a higher incidence of preterm birth, placental site disorders, antepartum haemorrhage, Caesarean section and neonatal unit admission. Failure to reach statisitical significance in our study may be due to small sample sizes in both groups. As the group without a diagnosis of endometriosis are likely to include some women with mild/minimal endometriosis, the findings of our study should be interpreted with caution in relatation to women with mild/minimal disease.

A further limitation of this study is that we included only live pregnancies that progressed beyond 12 weeks' 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 limited sample size in our study population may lead to non-statistically 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 low prevalence. The odds ratio for secondary outcomes that have high prevalence in the study population, specifically Caesarean

section delivery and postpartum haemorrhage, may be overestimated by logistic regression analysis and should be interpreted with this in mind.

Interpretation of results

Meta-analyses performed by Zullo et al (2017), Lalani et al (2018) and Breintoft et al (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)(21-23). The 24 studies included by Zullo et al (2017), 23 studies included by Lalani et al (2018) and 39 studies included by Brentoft et al (2021) were heterogenous in their methodology and diagnostic criteria, with mode of coneption 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 (PGE2, COX-2, interleukin-8) in peritoneal fluid of women with endometriosis, causing uterine muscle contraction and cervical ripening and progesterone resistence of the endometrium interfering with placentation(24, 25). Our study reported an odds ratio of similar magnitude to previous literature and suggests there may be an association with endometriosis and preterm birth. However, our results did not reach the threshold of significance on multivariable analysis, where mode of conception and presence of concurrent uterine abnormalities were considered. We did not demonstrate a significant association when considering subtype of endometriosis, previous surgical excision or mode of diagnosis. Exacoustos et al (2016) demonstrated the strongest association between presence of endometriosis and preterm birth, with an odds ratio of 6.87 (95% CI 3.07-15.36) for women with persistent rectovaginal endometriosis after

surgery(26). Farella et al (2020) also demonstrate a higher prevalence of preterm birth in women with a history of surgical management of endometriosis, especially in those with deep disease of the rectum or bladder, but their results may have been affected by a high incidence of ART conception within their population(27). In our subgroup analysis of women with residual or recurrent disease, we did not observe higher odds of preterm delivery. Glavind et al (2017) reported increased odds of preterm delivery, irrespective of mode of conception, with the risk being highest for very preterm birth (aOR 1.91 (95% CI 1.16-3.15) (28).

This study demonstrates higher odds of postpartum haemorrhage for women with endometriosis who were delivered by Caesarean section. Our findings are in agreement with Saraswat et al (2017), Yi et al (2020) and Velez et al (2022) who reported an increased risk of PPH with a diagnosis of endometriosis, but differ from the meta-analyses published by Horton et al (2019), Lalani et al (2018) and Breintoft et al (2021), who found that endometriosis was not associated with postpartum haemorrhage(10, 21, 23, 29-31). Theories that may support excessive blood loss at Caesarean section include angiogenesis, a possible association with mild bleeding disorders, pelvic adhesions, surgical complexity, increased operating time or bleeding from endometriotic deposits(32, 33). Decidualisation 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 oedema of lesions may also contribute to intraoperative blood loss(34-36). Some women that 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 exteriorisation of the uterus through the abdominal incision at Caesarean section could be most at risk. Intrapartum sepsis is commonly acknowledged as a risk factor for post partum haemorrhage, and although we demonstrated higher odds of post partum haemorrhage in women with endometriosis compared to those without, higher odds of intrapartum sepsis was only identified in those with persistent deep endometriosis after surgery. This is in keeping with data published by Lafleur et al (2022) in a cohort of women with active endometriosis in pregnancy following previous surgery(38).

Our study showed higher odds of newborn admission to the neonatal unit for babies 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 a small for gestational age baby. These findings are in agreement with Horton et al (2019), who also reported higher odds of NNU admission for women with endometriosis (OR 1.29; 95%CI 1.07-1.55; 5 studies), but no increased risk of SGA(29).

On univariate analysis, our study showed that women with endometriosis had higher odds of Caesarean section delivery. The odds of Caesarean section delivery were similar to that presented in existing published literature (OR 1.86; 95%CI 1.51-2.29; 20 studies)(21). Maggiore et al suspected that previous surgical intervention may be a contributing factor for the increased risk of Caesarean section delivery in women with endometriosis(39). On 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 (2000) suggested a possible explanation of abnormal uterine contractions, observed in women with endometriosis, leading to abnormal blastocyst implantation(40).

We did not demonstrate any statistically significant association between the presence of endometriosis and antepartum haemorrhage, placental abruption, gestational diabetes or hypertensive disorders of pregnancy. This is in keeping with previous studies(5, 29, 39).

Lalani et al (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(21). Breintoft et al (2021) also demonstrated increased odds of stillbirth (OR 1.27 (95% CI 1.07-1.51) (23). Although our study detected no association, both outcomes are uncommon, effecting <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' 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 two groups.

Several case reports describe uterine rupture, spontaneous haemoperitoneum, 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 ESHRE 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 pre-conceptually or in early pregnancy.

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602 # Figure captions

603 Figure 1: Flowchart showing inclusion of study participants (n = 503)

604

Tables

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 (years)	34 (22 – 44)	32 (16 – 49)
BMI (kg/m2)	23.7 (16.6 – 42.2)	23.9 (15.8 – 54.8)
Smoking status	5 (4.5)	27 (6.9)
Self-reported ethnicity		
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		
0	77 (70.0)	211 (53.7)
1	27 (24.5)	118 (30.0)
≥2	6 (5.5)	64 (16.3)
Gravidity		
1	52 (47.3)	126 (32.1)
2	30 (27.3)	121 (30.8)
≥3	28 (25.5)	146 (37.2)
ART conception	29 (26.4)	25 (6.4)
Multiple pregnancy	8 (7.3)	17 (4.3)
Gynaecological history		
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		
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)

Data are given as median (range) or n (%). Early miscarriage defined as <15+0 weeks gestation; Recurrent miscarriage defined as >/= 3 miscarriages;

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)	***No endometriosis*** (n = 393)	P*	OR (95% CI)	aOR (95% CI)
PTB (23+0 to 36+6 weeks)	13/109 (11.9)	25/391 (6.4)	0.065	1.98 (0.98 – 4.02)	†1.85 (0.50 – 6.90)
Late miscarriage (15+1 to 22+6 weeks)	1/110 (0.9)	2/393 (0.5)	>0.999	1.79 (0.16 – 19.67)	
Placenta Preavia/Accreta	3/109 (2.8)	3/391 (0.8)	0.121	3.66 (0.73 – 18.40)	
Placenta Praevia	2/109 (1.8)	3/391 (0.8)	0.590	2.42 (0.40 – 14.65)	
Placenta Accreta	1/109 (0.9)	0/391 (0.0)	0.218	-	
APH/Abruption	2/109 (1.8)	7/391 (1.8)	>0.999	1.03 (0.21 – 5.01)	
Hypertensive disorders of pregnancy	8/109 (7.3)	11/391 (2.8)	**0.011**	**3.79 (1.39 – 10.35)**	‡3.08 (0.99 – 9.62)
PIH	7/109 (6.4)	8/391 (2.0)	**0.026**	**3.29 (1.16 – 9.27)**	‡2.32 (0.69 – 7.74)
PET	4/109 (3.7)	6/391 (1.5)	0.236	2.44 (0.68 – 8.82)	
GDM	10/109 (9.2)	35/391 (9.0)	>0.999	1.03 (0.49 – 2.15)	
Intrapartum sepsis	7/109 (6.4)	17/391 (4.3)	0.445	1.51 (0.61 – 3.74)	
NNU admission	14/109 (12.8)	25/389 (6.4)	**0.041**	**2.16 (1.08 – 4.31)**	**§3.24 (1.08 – 9.73)**
SGA	6/109 (5.5)	41/391 (10.5)	0.138	0.50 (0.21 – 1.20)	
Caesarean section	56/109 (51.4)	145/391 (37.1)	**0.008**	**1.79 (1.17 – 2.75)**	‡1.26 (0.78 – 2.04)
Emergency CS	33/109 (30.3)	82/391 (21.0)	**0.053**	**1.64 (1.02 – 2.63)**	‡1.46 (0.86 – 2.47)
Elective CS	23/109 (21.1)	63/391 (16.1)	0.251	1.39 (0.82 – 2.37)	
PPH	57/109 (52.3)	117/391 (29.9)	**<0.001**	**2.57 (1.66 – 3.96)**	‡**2.44 (1.50 – 3.97)**
Vaginal delivery	17/109 (15.6)	70/391 (17.9)	0.699	0.85 (0.48 – 1.51)	
Caesarean section	40/109 (36.7)	47/391 (12.0)	**<0.001**	**4.24 (2.59 – 6.96)**	‡**3.64 (2.07 – 6.35)**

Data are given as n/N (%). *Fischer's exact test; OR, odds ratio; aOR, adjusted odds ratio; PTB, preterm birth; APH, antepartum haemorrhage; PIH, pregnancy induced hypertension; PET, pre-eclampsia; GDM, gestational diabetes mellitus; SGA, small for gestational age neonate; CS, Caesarean section; PPH, postpartum haemorrhage >500ml. † aOR adjusted for age, ART conception and concurrent presence of uterine adenomyosis, ‡ aOR adjusted for age, gravidity, ART conception, history of early miscarriage, previous pelvic surgery and concurrent presence of uterine adenomyosis, § adjusted for Caesarean section delivery

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)*	*Residual or recurrent DE (n = 24)*	P*	OR (95% CI)	aOR (95% CI)
PTB (23+0 to 36+6 weeks)	25/391 (6.4)	4/23 (17.4)	0.068	3.08 (0.97-9.75)	†1.86 (0.50-6.90)
Late miscarriage (15+1 to 22+6 weeks)	2/393 (0.5)	1/24 (4.2)	0.163	8.50 (0.74-97.23)	†7.33 (0.28-194.29)
Placenta Praevia/Accreta	3/391 (0.8)	3/23 (13.0)	**0.003**	**19.40 (3.68-102.26)**	**†8.65 (1.17-63.71)**
APH/Abruption	7/391 (1.8)	1/23 (4.4)	0.370	2.49 (0.29-21.17)	
Hypertensive disorders of pregnancy	11/391 (2.8)	2/23 (8.7)	0.101	4.56 (0.91-22.82)	‡1.30 (0.09-19.3)
GDM	25/391 (9.0)	2/23 (8.7)	>0.999	0.97 (0.21-4.30)	
Intrapartum sepsis	17/391 (4.3)	4/23 (17.4)	**0.023**	**4.63 (1.42-15.11)**	**§3.47 (1.02-11.75)**
NNU admission	25/389 (6.4)	5/23 (21.7)	**0.019**	**4.07 (1.39-11.86)**	**§3.24 (1.08-9.73)**
SGA	41/391 (10.5)	2/23 (8.7)	>0.999	0.81 (0.18-3.59)	
Caesarean section delivery	145/391 (37.1)	14/23 (60.9)	**0.028**	**2.64 (1.11-6.25)**	‡1.48 (0.44-5.04)
PPH	117/391 (29.9)	14/23 (60.9)	**0.003**	**3.64 (1.53-8.65)**	**‡6.20 (1.55-24.89)**

Data are given as n/N (%). *Fisher's exact test; PTB, preterm birth; APH, antepartum haemorrhage; GDM, gestational diabetes mellitus; NNU, neonatal unit admission; SGA, small for gestational age neonate; PPH, postpartum haemorrhage. † aOR adjusted for age, ART conception and concurrent presence of uterine adenomyosis, ‡ aOR adjusted for age, gravidity, ART conception, history of early miscarriage, previous pelvic surgery and concurrent presence of uterine adenomyosis, § adjusted for Caesarean section delivery.

Supplemental table 1 Primary indication for first clinic visit in 110 women with endometriosis and 393 women without a diagnosis of endometriosis (n = 503)

Indication	***Endometriosis (n = 110)***	***No endometriosis*** *(n = 393)*
Pelvic pain	31 (28.2)	150 (38.2)
Vaginal bleeding	26 (23.6)	94 (23.9)
Reassurance scan (asymptomatic)	32 (29.1)	83 (21.2)
Pelvic pain and vaginal bleeding	14 (12.7)	65 (16.5)
Referral from family planning clinic for suspected ectopic pregnancy	0 (0.0)	1 (0.3)
Referral from antenatal clinic with suspected adnexal lesion	7 (6.4)	0 (0.0)

Data are given as *n* (%).

Supplemental table 2 Concomitant congenital and acquired uterine abnormalities in 110 women with endometriosis and 393 women without a diagnosis of endometriosis (n = 503)

Concomitant uterine abnormality	**Endometriosis (n = 110)**	**No endometriosis (n = 393)**	**P***	**OR (95% CI)**
No uterine abnormality	77 (70.0)	340 (86.5)	**<0.001**	**0.36 (0.22-0.60)**
Uterine fibroids	25 (22.7)	46 (11.7)	**0.005**	**2.22 (1.29-3.81)**
Adenomyosis	10 (9.1)	6 (1.5)	**<0.001**	**6.45 (2.29-18.17)**
Major Congenital Uterine Anomaly	3 (2.7)	5 (1.3)	0.381	2.18 (0.51-9.25)
Subseptate	3	2		
Unicornuate	0	2		
Bicornuate	0	1		

Data are given as n (%). *Fischer's exact test

Supplementaal table 3 Indications for Caesarean section delivery in all women with a pregnancy progressing beyond 23 weeks' completed gestation (n = 500)

	Endometriosis (n=109)	***No endometriosis (n = 391)***	***P****
Emergency CS	33 (30.3)	82 (21.0)	0.053
Elective CS	23 (21.1)	63 (16.1)	0.251
Previous CS	8 (7.3)	26 (6.6)	0.830
Maternal request	3 (2.8)	4 (1.0)	0.356
Other indication	12 (11.0)	33 (8.4)	0.449

Data are given as *n* (%). ***** Fischer's exact test; CS, Caesarean section; Other indication includes breech presentation, multiple pregnancy, diabetes mellitus, recurrent miscarriage, maternal age and ART, previous vaginal prolapse surgery, previous excision of rudimentary uterine horn, pre-eclampsia, epilepsy

Supplemental table 4 Intrapartum and postpartum complications for women with and without a diagnosis of endometriosis (n = 503)

Indication	***Endometriosis (n = 110)***	***No endometriosis (n = 393)***
Post operative ileus	2 (1.8)	0 (0.0)
Return to theatre	1 (0.9)	1 (0.3)
Readmission to hospital	3 (2.7)	5 (1.3)
Bladder injury during CS	0 (0.0)	0 (0.0)
Bowel injury during CS	0 (0.0)	0 (0.0)
CS hysterectomy	0 (0.0)	0 (0.0)

Data are given as *n* (%); CS, Caesarean section.

Supplemental table 5 Obstetric and neonatal outcomes in 110 women with endometriosis, according to presence or absence of deep disease

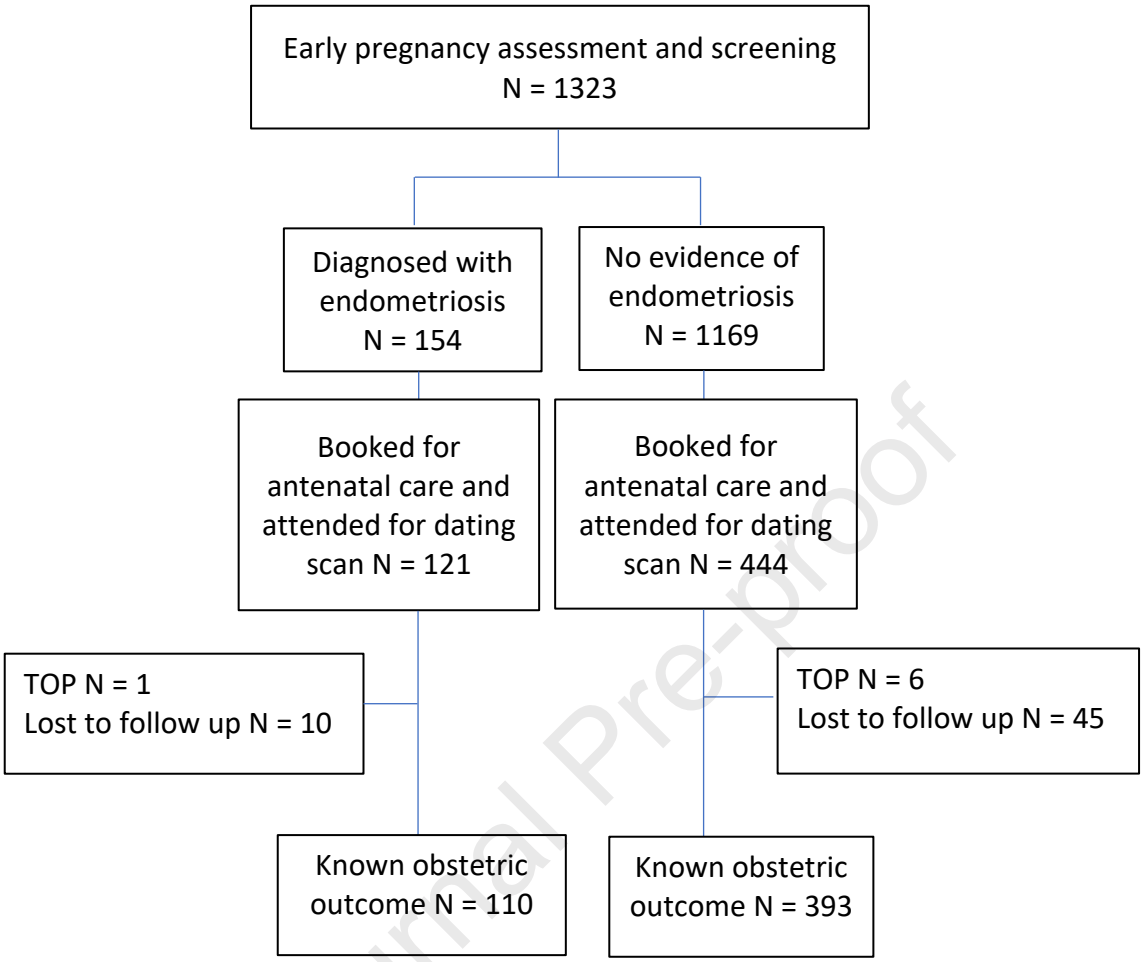
Outcome	***No deep endometriosis (n = 35)***	***Deep endometriosis (n = 75)***	**P***
PTB (23+0 to 36+6 weeks)	4/35 (11.4)	9/74 (12.2)	>0.999
Late miscarriage (15+1 to 22+6 weeks)	0/35 (0.0)	1/75 (1.3)	>0.999
Placenta Praevia/Accreta	0/35 (0.0)	3/74 (4.1)	0.550
APH/Abruption	1/35 (2.9)	1/74 (1.4)	0.541
Hypertensive disorders of pregnancy	3/35 (8.6)	5/74 (6.8)	0.710
GDM	1/35 (2.9)	9/74 (12.2)	0.163
NNU admission	4/35 (11.4)	10/74 (13.5)	>0.999
SGA	0/35 (0.0)	6/74 (8.1)	0.174
Caesarean section delivery	18/35 (51.4)	38/74 (51.4)	>0.999
PPH	16/35 (45.7)	41/74 (55.4)	0.413

Data are given as n (%); ***** Fisher's exact test; PTB, preterm birth; APH, antepartum haemorrhage; GDM, gestational diabetes mellitus; NNU, neonatal unit admission; SGA, small for gestational age neonate; PPH, postpartum haemorrhage.

Supplemental table 6 Obstetric and neonatal outcomes in 110 women with endometriosis, according to presence or absence of surgical confirmation of endometriosis

Outcome	***Surgical confirmation of endometriosis (n = 35)***	***Ultrasound diagnosis of endometriosis alone (n = 75)***	**P***
PTB (23+0 to 36+6 weeks)	5 (13.9)	8 (10.8)	0.64
Late miscarriage (15+1 to 22+6 weeks)	1 (2.8)	0 (0.0)	0.26
Placenta Praevia/Accreta	3 (8.3)	0 (0.0)	0.07
APH/Abruption	1 (2.8)	1 (1.4)	0.61
Hypertensive disorders of pregnancy	2 (5.6)	6 (8.1)	0.63
GDM	2 (5.6)	8 (10.8)	0.38
NNU admission	5 (13.9)	9 (12.2)	0.80
SGA	2 (5.6)	5 (5.4)	0.97
Caesarean section delivery	21 (58.3)	35 (47.3)	0.28
PPH	17 (47.2)	49 (66.2)	0.06

Data are given as n (%); ***** Fisher's exact test; PTB, preterm birth; APH, antepartum haemorrhage; GDM, gestational diabetes mellitus; NNU, neonatal unit admission; SGA, small for gestational age neonate; PPH, postpartum haemorrhage.



TOP, Termination of pregnancy