DOI: 10.1111/tog.12831
The Obstetrician & Gynaecologist
http://onlinetog.org
2022;24:242–50

Review

Obstetric and perinatal outcomes in women with endometriosis

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Accepted on 30 September 2021. Published online 11 September 2022.

Key content

- Endometriosis in pregnancy is associated with an increased risk of spontaneous miscarriage, pre-eclampsia, postpartum haemorrhage, caesarean section, placenta praevia, fetal growth restriction, prematurity and adverse neonatal outcomes.
- Women with mild disease are considered as having 'low-risk endometriosis' (LRE) and can expect a normal pregnancy and labour.
- The 'high-risk endometriosis' (HRE) group may require additional antenatal and intrapartum specialist care.

Learning objectives

- To understand the pathophysiologic basis of adverse obstetric and perinatal outcomes in pregnant women with endometriosis.
- To understand the obstetric outcomes in relation to the severity and staging of endometriosis.
- To appreciate the risk of spontaneous haemoperitoneum in pregnancy (SHiP) associated with endometriosis in pregnancy.

Keywords: adenomyosis / endometriosis / perinatal / pregnancy / SHiP

Please cite this paper as: Rafi J, Pathiraja PDM, Gelson E, Brown R, Alleemudder D. Obstetric and perinatal outcomes in women with endometriosis. *The Obstetrician & Gynaecologist* 2022;24:242–50. https://doi.org/10.1111/tog.12831

Introduction

Endometriosis is the growth of endometrial tissue outside of the uterus. It affects around 10% of women, and 30% of those affected will present with subfertility.[1] Endometriosis has a negative impact on both assisted and natural conception. Mechanisms proposed to account for fertility impairment include altered folliculogenesis resulting in ovulatory dysfunction and poor oocyte quality, as well as luteal phase defects, reduced fertilsation and abnormal embryogenesis.[2]

The presence of endometriosis may not only affect conception, but can also affect obstetric and neonatal outcomes in pregnancy. Here, we review the evidence supporting this hypothesis.

Feasibility of measuring obstetric and neonatal outcomes in those with endometriosis

Previous studies have been based upon either personal histories of endometriosis or have involved retrospective case note reviews. This makes correlations with obstetric outcomes difficult to interpret owing to variations in both the diagnostic criteria used or treatments undertaken before pregnancy. An international consensus study in 2020[3] aimed to standardise data collection and reporting as well as outcome selection across future randomised controlled trials (RCTs) and systematic reviews. The final consensus was based upon the following obstetric outcomes, including viable intrauterine pregnancy confirmed by ultrasound; pregnancy loss including ectopic pregnancy, miscarriage, still birth and termination of pregnancy; live birth; time to pregnancy leading to live birth; gestational age at delivery; neonatal mortality; and major congenital abnormalities.[3]

Pathophysiology of adverse obstetric outcomes

The pathophysiological mechanisms by which endometriosis is thought to affect obstetric outcomes include secretory phase endometrial milieu changes (specifically endometrial proliferation, glycosylation and progesterone resistance),

altered junctional zone functionality, uterine hyper contractility, genotoxicity and chronic inflammation.

Secretory phase endometrial milieu changes

Altered endometrial proliferation

The endometrial thickness typically increases up to 10 mm during the proliferative phase of the menstrual cycle. Endometrial thickness is reduced in women with endometriosis, resulting in an increased risk of implantation failure.[4]

Altered glycosylation

Endometrial receptivity primarily depends on the presence of surface glycoproteins within the glycocalyx of endometrial cells.[5] Glycosylation of the surface proteins is altered in endometriosis, affecting blastocyst interaction and reducing the likelihood of implantation.[6]

Progesterone resistance

Progesterone is implicated in halting estrogen-driven endometrial proliferation, recruitment of specialised immune cells to support embryonic implantation and preparation of the endometrium for implantation (decidualisation).

Two isoforms of progesterone receptors (PR-A and PR-B), located on stromal cells, mediate the effects of progesterone by causing secretion of paracrine factors and upregulating the enzyme 17β-hydroxysteroid dehydrogenase type 2 (17βHSD2). 17βHSD2 metabolises estrogen E2 to the weakly estrogenic estrone. There is downregulation of 17βHSD2 and decreased expression of PR-B in stromal cells in endometriosis. This leads to a progesterone-resistant state, causing impaired transformation of stromal cells into specialised decidual cells, resulting in impaired implantation.[7]

Genotoxicity

Oxidative stress is the imbalance between reactive oxygen species (ROS) and antioxidants (superoxide dismutase, catalase and glutathione peroxidase, and vitamin E and vitamin C). The connection between endometriosis and increased ROS production is well established[8] and it has been postulated as one of the central phenomena involved in maternal endothelial dysfunction and consequent adverse obstetric sequelae, such as pre-eclampsia (PET).[9] Another genotoxic mechanism involves the high iron content found within ovarian endometriomas, with consequent effects on developing oocytes, which may help to explain the higher miscarriage rate in nulliparous women.[10]

Altered junctional zone and defective implantation

The subendothelial myometrium (also known as the junctional zone) is a radiologically identified zone that is architecturally and functionally distinct from the outer myometrium.[11] The posterior junctional zone appears thickened on three-dimensional (3D) ultrasound and magnetic resonance imaging (MRI) in cases of adenomyosis, which may itself be related to abnormal basal invasion of the myometrium by this layer. The thickness of this layer has been associated with failure of implantation.[12]

Altered junctional zone and defective placentation

The uterine junctional zone, which becomes the primary site of the placental bed, is characterised during pregnancy by the remodelling of the spiral arteries into large uteroplacental vessels. Junctional zone disorders, together with the local endometrial proinflammatory state associated with endometriosis, may influence the decidua/trophoblast interactions contributing to various placental disorders.

For example, together with other factors such as uterine hyperperistalsis (itself associated with the development of endometriosis and adenomyosis), abnormal blastocyst implantation or the presence of dense pelvic adhesions, this may inhibit the uterine migration of the placenta, increasing the risk of placenta praevia.[13]

Defective placentation may result from partial or absent remodelling.[14] Whereas absent remodelling is predominantly seen with PET, partial vascular remodelling, which is seen in association with endometriosis, may lead to an increased risk of preterm birth, premature rupture of membranes (PROM) and fetal growth restriction.[14] Junctional zone disorders, together with the local endometrial proinflammatory state associated with endometriosis, may further influence the decidua/trophoblast interactions, also increasing the risks of preterm birth.[15]

Inflammation

Many studies have demonstrated high levels of inflammatory mediators such as cytokines,[16] IL-6,[17] IL-8[18] and prostaglandins[19] in the peritoneal fluid of women with endometriosis.

Furthermore, androgens are aromatised to estrogens by estrogen synthetase. This enzyme is absent in the normal endometrium but is abundant in endometriosis. In response to estrogen and accelerated through a positive feedback loop, cyclooxygenase-2 (COX-2) increases the production of prostaglandin E2 (PGE2) and prostaglandin F2α (PGF2α),[20] which potentiate the risk of uterine contractions, cervical ripening and preterm birth.[15] Table 1 summarises the pathophysiologic factors associated with endometriosis and the effects that these may have on pregnancy outcomes.

Adverse perinatal outcomes

Pre-eclampsia and gestational hypertension

The overall association between PET and endometriosis is not definitively established. In some studies, such as Zullo

Table 1. Pathophysiology and adverse obstetric outcomes in endometriosis

Mechanism	Resulting pregnancy complication	Effect
Secretory phase endometrial milieu changes • Altered endometrial proliferation* • Altered glycosylation* • Progesterone resistance (PRB isoform ↓, 17βHSD2 ↓)* • Altered junctional zone*	Defective implantation	Placenta praevia* Miscarriage Recurrent pregnancy loss
Genotoxicity (oxidative stress*; iron**) Inflammation (prostaglandins, IL-6, IL-8, cytokines)* Altered junctional zone and vasculature bed remodelling*	Defective placentation	Small for gestational age/fetal growth restriction* Pre-eclampsia* Preterm birth*
Endometriotic decidualised implant involution (triggered by progesterone resistance) surrounding distended vessels***	Vessel wall fragility resulting in spontaneous rupture of vessels***	Spontaneous haemoperitoneum in pregnancy***

*Common; **rare; ***very rare.

et al.,[21] no association with endometriosis was identified. Other studies have identified a modest association; for example, Lalani et al.[22] (odds ratio [OR] for PET of 1.18; 95% confidence interval [CI] 1.01–1.39, and for a composite of gestational hypertension and/or PET of 1.21; 95% CI 1.05–1.39) and Epelboin et al.[13] (OR for PET of 1.29).

Placenta praevia

Overall, endometriosis is associated with an increased risk of placenta praevia (OR 3.17; 95% CI 2.58−3.89).[23] Treatment with assisted reproductive technology (ART) by itself is associated with an increased incidence of placenta praevia (OR for singleton pregnancies of 5.6; 95% CI 4.4–7.0 after adjustment for confounders).[24] Data suggest that even among women who have conceived through ART, the risk is further increased in those with endometriosis (OR 2.96; 95% CI 1.25–7.03).[25]

Metabolic complications

In some studies, women with endometriosis have been identified to have increased risks for gestational diabetes mellitus (GDM) (OR 1.26; 95% CI 1.03–1.55) and cholestasis of pregnancy (OR 4.87; 95% CI 1.85–12.83),[22] with higher risks for GDM in spontaneous conceptions than those achieved through in vitro fertilisation (IVF).[13]

Fetal and neonatal outcome

Fetuses and neonates of women with endometriosis were also more likely to have preterm premature rupture of membranes (PPROM) (OR 2.33; 95% CI 1.39–3.90), preterm birth (OR 1.70; 95% CI 1.40–2.06), small-for-gestational-age fetuses below the 10th percentile (OR 1.28; 95% CI 1.11–1.49), admission to the neonatal intensive care unit (NICU) (OR 1.39; 95% CI 1.08–1.78), stillbirth (OR 1.29; 95% CI 1.10–1.52) and neonatal death (median odds ratio [MOR] 1.78; 95% CI 1.46–2.16).[22] Among the subgroup of women who conceived spontaneously, endometriosis was associated with placenta praevia, caesarean section, preterm birth and low birthweight. Among the subgroup of women who conceived with the use of ART, endometriosis was associated with placenta praevia and preterm birth.

Spontaneous haemorrhage in pregnancy

Spontaneous haemoperitoneum in pregnancy (SHiP; see Box 1) is characterised by unprovoked intraperitoneal bleeding with an incidence rate of 1:10 000 pregnancies.[36] Endometriosis is associated with 19%[36] to 55.9%[37] cases of SHiP. The correlation between the stage of endometriosis and incidence of SHiP remains unknown. While maternal mortality associated with SHiP fell dramatically between 1950 and 1987, fetal mortality remains high at 31%.[31] Of

Box 1. Pathophysiology of spontaneous haemoperitoneum in pregnancy (SHiP)

Endometriotic decidualised implant invasion
Affecting the appendix***,[26] terminal ileum***,[27] and colon***,[28] causing tissue perforation with severe gastrointestinal bleeding[29] or urohaemoperitoneum*** with urinary tract endometriosis[30]
Involution of decidualised (progesterone mediated*)
endometriotic implants associated with parametrial veins causing vascular fragility and spontaneous peritoneal bleeding***[31]
Uterine rupture***[32,33] in nulliparous women both before and during labour or uterine scar weakness following excision of rectovaginal nodule[34] or electrosurgical treatment[23] of stage 4 endometriosis.
Chronic inflammation* causes tissues affected by endometriosis to be more friable. The combined presence of pelvic adhesions and an increasing uterine volume places the vessels at risk of tearing***[35]
*Common; **rare; ***very rare.

such cases, 61% occur antenatally in the third trimester, 18% intrapartum, and 21% up to 42 days postpartum.[38] A review of 21 studies[31] showed that 72% were nulliparous presenting with sudden onset of nonspecific abdominal pain (95%) and signs of hypovolemic shock (70%). Rare presentations include a gradual fall in haemoglobin and tachypnoea caused by a haemothorax.[38] The diagnosis of SHiP is largely established at laparotomy undertaken for maternal reasons (hypovolemic shock and suspected haemorrhage) or fetal hypoxia.

Implications of endometriosis for care during pregnancy

Most women with mild disease are considered as having 'low-risk endometriosis' (LRE) and can expect a normal pregnancy and labour. The 'high-risk endometriosis' (HRE) group require additional antenatal and intrapartum specialist care. This group includes women with adenomyosis, conception by assisted reproduction, or those surgically treated for peritoneal and deep infiltrating endometriosis (DIE) (e.g., rectovaginal nodules).

Women with HRE should receive prenatal counselling and be considered higher risk in pregnancy and at delivery.[35,39] However, there is currently no national or international guidance. Here, we suggest a possible plan for such counselling (see also Figure 1).

Preconception counselling for women identified as HRE

Women in the HRE group sometimes present with longstanding infertility issues and are desperate to achieve a successful pregnancy. It is usually agreed that their family unit should be complete before embarking upon definitive surgery for endometriosis. Women in this group should be allowed to make informed choices based on their priorities and preferences. The objective of achieving a successful pregnancy should not discount the risks associated with pregnancy and labour. Women should be counselled regarding the following:

- Women with endometriosis/adenomyosis conceiving spontaneously have an increased risk of miscarriages, pregnancy-induced hypertension, PET, small-for-gestational-age fetuses, preterm delivery, caesarean section and neonatal admissions[13,22,35]
- Women with endometriosis conceiving with ART have a 38% increased risk of preterm delivery, 18% higher risk of PET, 87% higher risk of placental abruption, 29% higher risk of neonatal unit admission, 25% higher risk of intrauterine death, a twofold increase in caesarean section and over threefold increased risk of placenta praevia.[13,22,35]

Antenatal care

Women with HRE should be managed within a consultant-led high-risk pregnancy clinic. A multidisciplinary approach may be required in specific cases, and this team might include a senior obstetrician, neonatologist, endometriosis specialist, interventional radiologist, haematologist, colorectal surgeon and urologist, as necessary.

Mental health and wellbeing must be considered because women with endometriosis (especially those who conceived with ART and posterior DIE) are at risk of, or may already be, experiencing mental health conditions such as anxiety and depression, which might deteriorate during pregnancy.

Blood flow within adenomyotic lesions is abundant, while placental blood flow may be reduced;[40] this may contribute to the increased risks of pregnancy-induced hypertension, PET and small-for-gestational-age fetuses in these women.[22,35,41–44] Furthermore, women presenting with diffuse adenomyosis have a significantly higher first-trimester and mid-pregnancy mean uterine artery doppler and lower first-trimester levels of pregnancy associated plasma protein-A (PAPP-A).[41] Although not evaluated in this specific population, low-dose aspirin may be beneficial. Serial growth scans and close surveillance of blood pressure are also advisable. Studies evaluating this are in progress.[45] The risk of preterm birth and PPROM in pregnant women with adenomyosis is also higher than those in women with endometriosis.[22,35,42–44,46–51] Preliminary data regarding assessment of uterine wall thickness has shown some promise in prediction of preterm delivery in these women.[52]

As noted above, endometriosis – and especially the combination of ART and endometriosis – increase the risk of placenta praevia. A comparison of diagnostic subgroups suggests that the risk of placenta praevia is 7.6% in patients with rectovaginal lesions and up to 2.4% in women with peritoneal and/or ovarian disease.[10,48] There is also increased risk of morbidly adherent placenta[53] in adenomyosis. Detailed placental evaluation must therefore be performed in these women.

Chronic pelvic pain from endometriosis can be exacerbated during pregnancy because of adhesions, bowel dysfunction, complications of endometriomas and pressure from the enlarging uterus (especially in those with posterior DIE).

Degeneration of adenomyomas, although rare, can be difficult to distinguish from chorioamnionitis, adenomyosis abscess formation or acute appendicitis in women presenting with fever, abdominal pain and raised inflammatory markers.[35,40]

Endometriomas can increase up to 20 cm during pregnancy. Torsion, cyst rupture or – rarely – an infected endometrioma can present with peritonitis and require surgery. Increased progesterone in pregnancy can also cause extensive decidualisation within a cyst, which can mimic

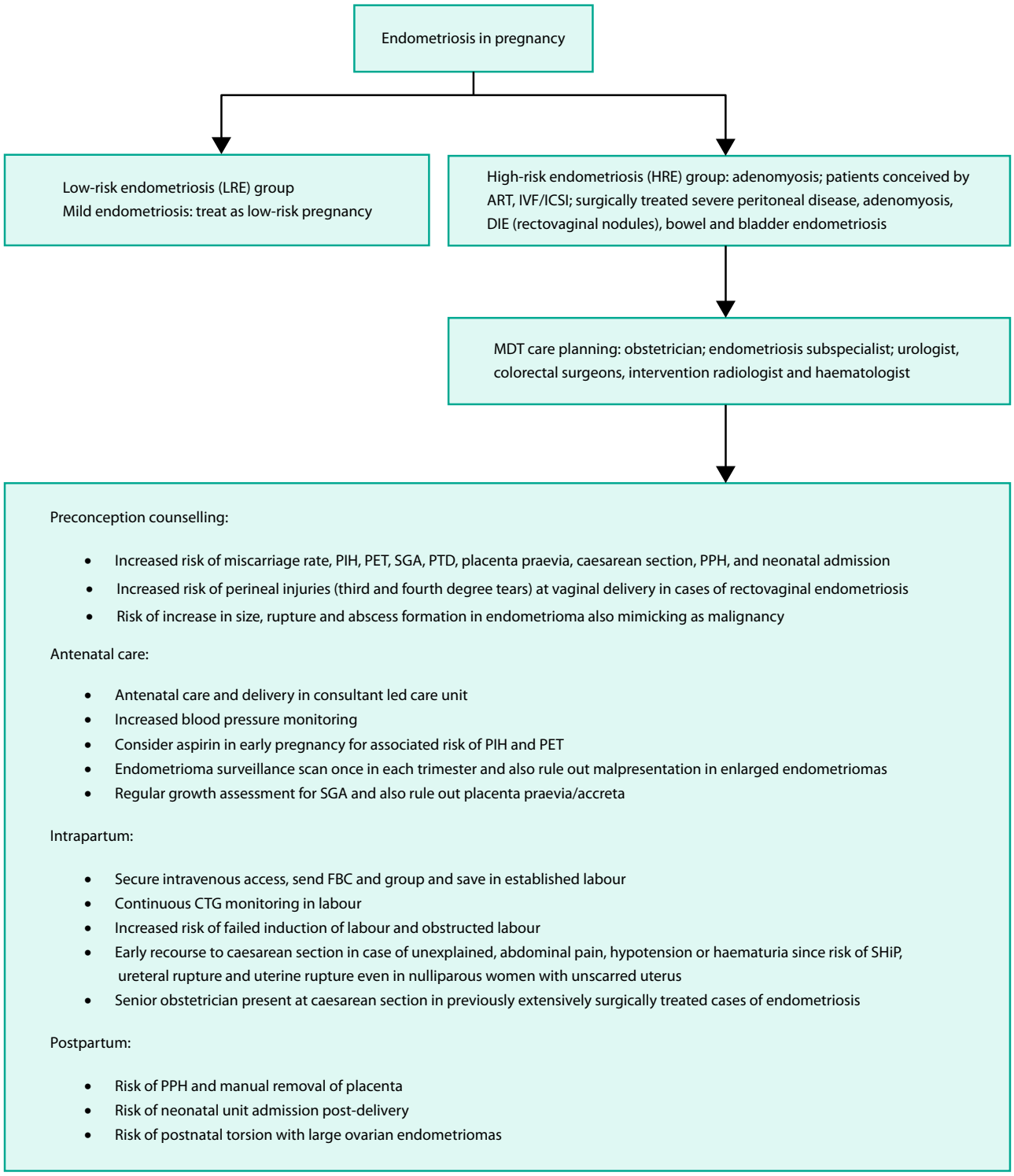

Figure 1. Suggested algorithm: management of high-risk endometriosis (HRE) disease spectrum in pregnancy. ART = assisted reproductive technology; DIE = deep infiltrating endometriosis; FBC = full blood count; MDT = multidisciplinary team; PIH = pregnancy-induced hypertension; PET = pre-eclampsia; PTD = preterm delivery; PPH = postpartum haemorrhage; SGA = small for gestational age; SHiP = spontaneous haemoperitoneum in pregnancy.

malignancy.[35] While ultrasound is the preferred imaging modality during pregnancy, MRI without gadolinium is advantageous where ultrasound is limited by the enlarged uterus and displaced ovaries. Laparoscopy is the preferred operative method prior to 23 weeks of gestation,[54,55] with laparoscopy being undertaken up to 34 weeks of gestation.[56]

Ureteral involvement in endometriosis can be found in 9–23% of cases, most often associated with ovarian endometriomas (in 52–68%) and deep infiltrating endometriotic implants (in 47–56%). Only 9–16% of these cases have urinary symptoms, but rarely can have significant associations including ureteric stenosis, hydroureter, hydronephrosis and renal damage.[57]

Intrapartum care and mode of delivery

Women in the HRE group should be advised to deliver within a consultant-led service.

Endometriosis can be associated with pelvic adhesions and distortion of the normal pelvic anatomy. Adenomyosis may increase malpresentation rates[58] and be associated with higher rates of failed induction and labour dystocia.[22,59] Prior uterine surgery affecting the myometrium may also increase the risk of uterine rupture.

There appears to be a higher risk of neonatal admissions in the HRE group following delivery (OR 1.29, 95% CI 1.07–1.55)[22,35,60] and women with endometriosis face not only an increased risk of stillbirth (OR 1.29; 95% CI 1.10–1.52),[22,39,61] but also of neonatal death (OR 1.78; 95% CI 1.46–2.16).[22,47] Therefore intravenous access should be gained and blood made available to anticipate the risk of placental abruption[35,47,49,61] and postpartum haemorrhage.[22,35,39,47,60–63] Continuous fetal heart rate monitoring is advisable in light of the increased frequency of fetal complications.

Most women will achieve a vaginal delivery, but patients should be counselled regarding the increased risk of perineal injuries (third and fourth degree tears), especially in association with rectovaginal endometriosis.[35,64] Large endometriomas can have a negative impact on vaginal delivery and have been implicated in obstructed labour. Endometriosis is also associated with an increased risk of breech presentation.[22,49,60,61]

The risk of caesarean delivery is, however, increased in those with endometriosis (OR 1.31; 95% CI 1.16–1.50).[21,22,35,48,60,62,63] Vercellini et al.[10] compared caesarean delivery rates with disease subtypes and demonstrated a frequency of 42.9% with rectovaginal endometriosis, 40.4% in those with ovarian endometriomas and peritoneal implants, 31.8% with peritoneal endometriosis and 20.5% with ovarian endometriosis. There is also an increased risk of caesarean delivery in women with deep infiltrative endometriosis of the anterior and posterior compartment, regardless of previous surgery.[49,65] A Swedish study[50] showed that the risk of prelabour caesarean delivery with endometriosis was higher (adjusted OR 1.64, 95% CI 1.54–1.75; $P < 0.05$) than for emergency caesarean delivery (adjusted OR 1.18; 95% CI 1.10–1.27; $P < 0.05$), after adjustment for maternal age, smoking, body mass index

Table 2. Summary of obstetric outcome evidence from systemic reviews/meta-analyses from 2017–2021

Reference	MMC	PTB < 37 weeks	SGA	PET	CD	PPH	PP	Malpresentation	NNU	SB
Zullu et al., 2017[21]	↑	↑	↑		↑		↑			
Glavind et al., 2018[67]		↑	↑							
Bruun et al., 2018[42]		↑	↑							
Perez-Lopez et al., 2018[43]		↑	↑							
Lalani et al., 2018[22]		↑	↑	↑	↑	↑	↑	↑	↑	↑
Razavi et al., 2019[63]		↑	↑		↑	↑				↑
Horton et al., 2019[35]	↑	↑	↑	↑	↑	↑	↑		↑	
Nirgianakis et al., 2020[60]	↑	↑	↑	↑	↑	↑		↑	↑	
Huang et al., 2020[39]	↑	↑				↑	↑			↑

Abbreviations: CD = caesarean delivery; NNU = neonatal unit admission; PET = pre-eclampsia; PP = placenta praevia; PPH = postpartum haemorrhage; PTB = preterm birth; SB = stillbirth; SGA = small for gestational age.
Upward arrow (↑) indicates increased incidence.

(BMI), parity, years of formal education and child's year of birth, but not for ART procedures.

A full picture of prior disease severity should be established early in pregnancy because it is crucial to anticipate potential challenges during a caesarean section. Some patients may have undergone endometriosis ablation, peritoneal stripping or dissection in close proximity to major ovarian/uterine vessels and structures, while others may have had more complex procedures such as colorectal resection or ureterovesical reimplantation. The pelvis can be obliterated in women with rectovaginal lesions, with the rectosigmoid being adherent to the posterior uterine wall.[10] Entry into the uterovesical space can be challenging in women with bladder endometriosis.

Opportunistic surgical treatment can be considered to remove large ovarian endometriomas at the time of planned elective caesarean section to avoid pain and torsion in postnatal period.

Postpartum care

Active management of the third stage of labour will help to reduce the risk of postpartum haemorrhage, anaemia and the need for blood transfusion.

Pregnancy creates a pseudomenopausal state, which helps remission of the disease, so patients should be informed that they may experience a recurrence of symptoms in the puerperium.

SHiP associated with mild endometriosis has also been described as late as day 9 postpartum,[66] and therefore unexplained abdominal pain or hypotensive after birth warrants investigation.

Conclusions

Available data identifies a higher risk of complications in pregnancy in women with significant prior endometriosis; this is summarised in Table 2. There is convincing evidence of an association between endometriosis and spontaneous miscarriage, preterm birth, small-for-gestational-age fetuses, placenta praevia, postpartum haemorrhage and caesarean birth. SHiP is a rare but potentially life-threatening consequence of endometriosis. Less certain is the association with PET/hypertension in pregnancy. The large multicentre centre study by Exacoustos et al.,[49] three large national studies by Berlac et al.,[47] Pan et al.,[68] and Epelboin et al.,[13] and meta-analyses by Horton et al.,[35] Lalani et al.,[22] Nirgianakis et al.[60] and Breintoft et al.[29] all suggest that women with prior endometriosis have higher rates of PET as well as hypertension in pregnancy. In contrast, meta-analyses by Zullu et al.,[21] Glavind et al.,[67] Brun et al.[42] and Perez et al.[43] showed no significant association.

Disclosure of interests

There are no conflicts of interest.

Contribution to authorship

JR conceived the idea and was involved in design, acquisition of data, drafting the article, table and algorithm creation and revised the article critically for important intellectual content. PDM was involved in drafting the article. EG revised the article critically for important intellectual content. RB and DA drafted the article and revised the article critically for important intellectual content. All authors approved the final version.

Acknowledgements

We thank Professor PJ Steer for his helpful editorial comments in the preparation of this article.

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