Impact of endometriosis and adenomyosis on pregnancy outcomes

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Endometriosis and adenomyosis not only cause symptoms such as dysmenorrhea, chronic pelvic pain, and infertility, but have also recently been implicated in a range of obstetric complications. The association between endometriosis and adenomyosis and adverse pregnancy outcomes has been developing as a new topic in the field of reproductive medicine over the past few years. This review aims to summarize in detail the latest evidence on the incidence of obstetric complications associated with endometriosis or adenomyosis and to discuss possible underlying pathophysiological mechanisms.

Introduction

Endometriosis and adenomyosis are both associated with chronic inflammation and cause disorders including dysmenorrhea, chronic pelvic pain, and infertility.1–4) Endometriosis is defined as the presence of endometrial tissue in areas outside of the uterus such as ovaries or fallopian tubes; adenomyosis is its presence specifically in the myometrium.5,6) Although these two disorders resemble each other in that they both involve the ectopic growth of endometrial tissue, they differ not only in the location of the growth but also in other characteristics, with adenomyosis being more common in women who have given birth and occurring at a later age compared to endometriosis.7) As the former is also associated with hyperplasia and fibrosis of the myometrium surrounding endometrial tissue, it is also regarded as a different disease entity with regard to pathology. One shared characteristic between the two is that they change in accordance with fluctuations in female hormones, and 6–20% of women with adenomyosis also suffer from endometriosis.7,8)

While several studies have reported that infertility is associated with endometriosis and adenomyosis,9–12) recent advances in infertility treatment have enabled women with these conditions to conceive successfully. Meanwhile, recent studies have found that endometriosis and adenomyosis not only affect infertility, but are associated with a range of obstetric complications after successful conception.13–18) This review article summarizes recent findings on the association between endometriosis and adenomyosis and obstetric complications.

Obstetric complications associated with endometriosis

In the past decade, numerous studies have noted an increase in the rates of a wide variety of obstetric complications, including premature rupture of membranes (PROM), preterm delivery, abnormal placental positioning, small for gestational age (SGA) infants, and preeclampsia (PE) in endometriosis patients.19–24) However, incidences of these complications vary widely and depend on patient characteristics, such as the severity of endometriosis and the rate of assisted reproductive technologies (ART) used to conceive.

In 2017, Zullo et al. published a meta-analysis of 24 studies that included 1.9 million women and compared obstetric complications in pregnant women with endometriosis to that of controls.25) They showed that incidences of abnormal placental positioning, SGA infants, and cesarean sections were higher in pregnant
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women with endometriosis, but found no increase in the incidence of hypertensive disorders of pregnancy (HDP) or PE. However, the meta-analysis did not analyze the rate of ART use or endometriosis subtypes. In 2018, Lalani et al. carried out a meta-analysis of 33 studies including 3.28 million women, who were divided into those who conceived naturally and those who used ART.26) The meta-analysis revealed that incidences of preterm delivery and abnormal placental positioning were higher in pregnant women with endometriosis in both natural conception and ART groups. The incidence of SGA infants was higher only in the natural conception group, and the incidence of HDP did not differ between groups.

With regard to the correlation with the severity of endometriosis, our colleagues Fujii et al. conducted a retrospective study of 631 women who became pregnant with ART and found that the severity of endometriosis may be associated with obstetric complications.27) They found no increase in the incidence of preterm delivery or abnormal placental positioning in stages I–III, although a marked increase in the incidence of both was observed in stage IV.

Endometriosis can be categorized into three distinct subtypes: peritoneal, ovarian, and deep infiltrating endometriosis. Deep infiltrating endometriosis lesions are characterized by penetration in excess of 5 mm under the peritoneal surface.28) More and more studies have also been investigating the effect of deep infiltrating endometriosis on obstetric complications. Despite some

Table 1. Studies showing pregnancy outcomes in women with adenomyosis

<table>
<thead>
<tr>
<th>Year</th>
<th>Study</th>
<th>Type of study</th>
<th>Study population</th>
<th>Outcomes</th>
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<tbody>
<tr>
<td>2006</td>
<td>Juang et al.</td>
<td>Nested case-control</td>
<td>104 women with preterm delivery vs 208 women who delivered at term</td>
<td>Increased risk of preterm birth (adjusted OR 1.8, 95% CI 1.3–4.3) and preterm PROM (adjusted OR 1.9, 95% CI 1.3–3.1)</td>
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<tr>
<td>2015</td>
<td>Mochimaru et al.</td>
<td>Case-control</td>
<td>36 women with adenomyosis vs 144 women without adenomyosis, diagnosed by MRI or transvaginal ultrasound</td>
<td>Increased risk of preterm birth (OR 5.0, 95% CI 2.2–11.4), preterm PROM (OR 5.5, 95% CI 1.7–17.7), SGA infants (OR 4.3, 95% CI 1.8–10.3), fetal malpresentation (OR 4.2, 95% CI 1.6–10.8), cesarean delivery (OR 4.5, 95% CI 2.1–9.7), and PPH (OR 6.5, 95% CI 2.2–19.0)</td>
</tr>
<tr>
<td>2017</td>
<td>Hashimoto et al.</td>
<td>Case-control</td>
<td>49 women with adenomyosis vs 245 women without adenomyosis, diagnosed by MRI or transvaginal ultrasound</td>
<td>Increased risk of preterm birth (OR 3.1, 95% CI 1.2–7.2), second trimester miscarriage (OR 21.0, 95% CI 2.2–71.2), SGA infants (OR 3.5, 95% CI 1.2–9.0), HDP (OR 6.7, 95% CI 2.7–18.2), placental malposition (OR 4.9, 95% CI 1.4–16.3), and cesarean delivery (OR 4.0, 95% CI 1.9–8.6)</td>
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<td>2017</td>
<td>Tamura et al.</td>
<td>Retrospective questionnaire survey</td>
<td>272 women with adenomyosis, identified according to the questionnaire survey from 65 facilities</td>
<td>Increased risk of second trimester miscarriage, cervical incompetency depending on size of adenomyosis, increased risk of preeclampsia, and uterine infection in diffuse type adenomyosis</td>
</tr>
<tr>
<td>2018</td>
<td>Shin et al.</td>
<td>Nested case-control</td>
<td>72 women with adenomyosis vs 8,244 women without adenomyosis, identified using computerized ultrasonography database</td>
<td>Increased risk of preterm birth (OR 3.3, 95% CI 1.6–6.8) and SGA infants (OR 5.0, 95% CI 2.5–9.9)</td>
</tr>
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<td>2018</td>
<td>Yamaguchi et al.</td>
<td>Prospective birth cohort study</td>
<td>314 women with adenomyosis vs 93,668 women without adenomyosis, identified using self-reported questionnaires</td>
<td>Increased risk of preterm birth (adjusted OR 2.4, 95% CI 1.8–3.4) and SGA infants (adjusted OR 1.6, 95% CI 1.1–2.5)</td>
</tr>
<tr>
<td>2019</td>
<td>Razavi et al.</td>
<td>Meta-analysis</td>
<td>Six studies (322 women with adenomyosis vs 9,420 without adenomyosis)</td>
<td>Increased risk of preterm birth (OR 3.0, 95% CI 2.0–4.47), SGA infants (OR 3.2, 95% CI 1.7–6.0), and preeclampsia (OR 4.3, 95% CI 1.0–17.7)</td>
</tr>
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OR, odds ratio; CI, confidence interval; PROM, premature rupture of membranes; PPH, postpartum hemorrhage; SGA, small for gestational age; HDP, hypertensive disorders of pregnancy
variation between studies, many have found that deep infiltrating endometriosis increases the rates of preterm delivery, SGA infants, abnormal placental positioning, PE, and other obstetric complications.\(^{29-31}\) However, most of those studies included adenomyosis in their classification of deep infiltrating endometriosis, and thus did not exclude the effect of adenomyosis on pregnancy. Further studies are needed to distinguish between the pathological influences of adenomyosis and deep infiltrating endometriosis on the onset of obstetric complications based on appropriate diagnostic imaging.

### Adenomyosis and obstetric complications

Compared to data obtained from numerous studies on endometriosis, not much is available concerning the association between adenomyosis and obstetric complications, with only six studies published in English to date (Table 1). The first study on adenomyosis and obstetric complications was published relatively recently, in 2006. Juang et al. compared 104 women who gave birth prematurely with a control group of 208 women with term deliveries and found that the adenomyosis group had a higher risk of PROM and preterm delivery.\(^{16}\) Subsequently, Mochimaru et al. conducted a retrospective comparative study of 36 pregnant women with adenomyosis and 144 without the disease and found that adenomyosis in pregnant women increased the rates of preterm delivery, PROM, SGA infants, fetal malpresentation, cesarean section, and postpartum hemorrhage (PPH).\(^{17}\) Because many pregnant women with adenomyosis are older, have a high rate of ART use, and are often primipara, we conducted a case-controlled study with a control group matched for these three factors. We compared 49 pregnant women with adenomyosis to a control group of 245 pregnant women and found that adenomyosis in pregnant women not only increases the rates of preterm delivery, SGA infants, and cesarean section, but also the incidence of late spontaneous abortion, abnormal placental positioning, and HDP.\(^{18}\) Tamura et al. reported the results of a national survey carried out in 2011 by the Japan Society of Obstetrics and Gynecology with the aim to investigate the prognosis of adenomyosis in pregnancy. They analyzed 262 cases of adenomyosis in pregnant women from 65 institutions and found that the greater the size of the adenomyosis (major axis >60 mm), the higher the rates of late spontaneous abortion and cervical incompetency, and that the rates of HDP and intrauterine infection were higher for women with diffuse adenomyosis compared with focal adenomyosis.\(^{32}\) Shin et al. compared 72 pregnant women with adenomyosis to a control group of 8,244 pregnant women and found that adenomyosis in pregnant women increased the rates of preterm delivery and SGA infants.\(^{33}\) In 2018, Yamaguchi et al. also reported an increased risk of preterm delivery and SGA infants with adenomyosis in pregnant women, comparing 314 women with adenomyosis to 93,668 women without adenomyosis in a prospective birth cohort study.\(^{34}\) Moreover, the most recent meta-analysis by Razavi et al. demonstrates that pregnant women with adenomyosis have an increased risk for preterm birth (OR, 3.05; 95% CI, 2.08–4.47), SGA infants (OR, 3.22; 95% CI, 1.71–6.08), and PE (OR, 4.35; 95% CI, 1.07–17.72).\(^{35}\)

Adenomyosis in pregnancy has thus been shown not only to increase incidences of preterm delivery, SGA infants, and abnormal placental positioning (as has been demonstrated in pregnant women with endometriosis), but also to increase the rates of other obstetric complications such as late spontaneous abortion, HDP, and fetal malpresentation.\(^{16-18,32-34}\) Since some of the previous reports on endometriosis have not excluded adenomyosis, interpretation of these data should include the consideration that adenomyosis may have been a confounding factor increasing the obstetric complications in those studies.

### Possible association between adenomyosis and HDP

As described above, pregnant women with adenomyosis may face a higher risk of developing HDP.\(^{18,32}\) The incidence of HDP is known to be higher in primipara and older gravida, but as mentioned earlier, our study matched participants for age, use of ART, and parity, and still found that the rate of HDP was higher in pregnant women with adenomyosis, indicating that adenomyosis itself is associated with the occurrence of HDP. When HDP was divided into gestational hypertension (GH), preeclampsia (PE), chronic hypertension (CH), and superimposed pre-eclampsia (SPE), we found that PE occurred significantly more frequently than the others.\(^{18}\) However, other studies have not found any increase in the rate of PE in pregnant women with adenomyosis. As mentioned above, it remains unclear whether endometriosis in pregnancy increases the incidence of HDP or PE or not, and a consensus has yet to be obtained. This may be because endometriosis and adenomyosis both have several different subtypes. A recent multicenter cohort study comparing 41 pregnant women with deep endometriosis to a control group of 300 pregnant women found that the rate of HDP was significantly higher among those with deep endometriosis.\(^{30}\) This suggests that the severity of endometriosis may have affected the development of HDP and that certain subtypes of endometriosis may increase the likelihood of developing HDP. The same can be true for adenomyosis, and it is possible that the incidence of adenomyosis might vary depending
on the conditions of the disease, such as the size and the lesion subtype (e.g., focal or diffuse type) or the use of previous treatment before conception. Further studies to identify associated factors which link adenomyosis to the development of HDP are warranted.

Speculation on the pathological mechanisms by which adenomyosis adversely affects pregnancy outcomes

Nothing is known about the mechanism of action by which adenomyosis is implicated in the development of various obstetric complications, including HDP. However, several studies have addressed the relationship between endometriosis and obstetric complications. Endometriosis in pregnant women has been shown to increase the rates of obstetric complications including not only PROM, preterm delivery, and placenta previa, but also other conditions such as SGA infants and PE. It has been suggested that endometriosis-induced chronic inflammation may exert adverse effects. Recent attention has been focused on disturbances in early placentaentation due to incomplete spiral artery remodeling, which has been implicated in PE and a wide range of other obstetric complications, including late spontaneous abortion, preterm delivery, and SGA infants. Since the prevalence of many of these disorders is also higher in those with adenomyosis, we speculate that a similar pathologic mechanism may be involved. In adenomyosis, chronic inflammation is believed to be present in the myometrium; this may exert a direct adverse effect on implantation and placentation (Figure 1). Implantation failure is associated with abnormal placentation positioning, and early incomplete placentation may contribute to the development of obstetric disorders such as PE and SGA infants. As Yorifuji et al. recently reported in a study using magnetic resonance angiography, the presence of adenomyosis can result in the reduction of placental blood flow leading to more infants with SGA. Thus, uteroplacental perfusion failure due to the presence of adenomyosis might also trigger placental ischemia associated with subsequent PE development. It is thought that adenomyosis may increase intrauterine pressure during pregnancy due to the poor muscular elasticity and insufficient expansion of the myometrium in accordance with the growing uterine content, which may contribute to cervical incompetency, late spontaneous abortion, and preterm delivery. This is a conjectural hypothesis, and its verification and the results of further studies are anticipated.

Figure 1. A hypothetical model of the pathophysiological involvement of adenomyosis in obstetrical complications.

Chronic inflammation in the myometrium induced by adenomyosis may be the central driving force in developing obstetric disorders associated with adenomyosis, including preterm birth, 2nd trimester miscarriage, and placenta-associated disorders such as placental malposition, preeclampsia, and SGA infants. Insufficient placentation associated with adenomyosis may also trigger placental dysfunction leading to such obstetric disorders.

Future perspectives for the management of pregnant women with adenomyosis

As discussed above, the incidence of HDP is higher in pregnant women with adenomyosis, who must therefore be managed as a group at high risk of developing HDP. Although further investigation is warranted, it is possible that prophylactic low-dose aspirin might be useful for preventing the development of PE in pregnant women with adenomyosis. Recent studies have shown that surgical removal of adenomyosis lesions improves adenomyosis-related clinical features, including infertility, dysmenorrhea, and hypermenorrhea. On the other hand, the incidence of uterine rupture during pregnancy or placenta accreta requires attention when treating pregnant women after the surgery. Considering these serious obstetric complications, it remains unclear whether improving fertility rates through the removal of adenomyosis would help ensure healthy offspring or not. Moreover, numerous reports focus on the incidence of uterine rupture following enucleation of adenomyosis, but the procedure may help in reducing adenomyosis-related obstetrical risks such as late spontaneous abortion, preterm labor, HDP, and placenta previa, so whether the beneficial effect of enucleation of adenomyosis outweighs the side effects of the procedure is an extremely interesting question meriting further study. In any case, pregnant women with adenomyosis must be managed carefully as high-risk pregnancy cases, with close consideration of the possibility of developing various pregnancy complications.
Conclusions

Recent studies have demonstrated that pregnant women with endometriosis or adenomyosis are more likely to present with a wide variety of pregnancy complications which could result in poor perinatal outcomes. Pregnant women with endometriosis or adenomyosis require even more careful perinatal management than previously thought. Further studies are needed to clarify the pathophysiologic mechanisms on how these disease conditions detrimentally affect the course of pregnancy. Moreover, from a clinical perspective, optimal management strategies for pregnant women with endometriosis or adenomyosis are required to achieve better perinatal outcomes.

Conflict of interest

None.

References


