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Association between endometriosis and perinatal complications: a case-control study

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Abstract

Background Recently, a history of endometriosis has been reported to be associated with several perinatal complications. However, it is unknown whether pre-pregnancy treatment for endometriosis reduces perinatal complications. In this study, we aimed to clarify the association between endometriosis and perinatal complications and investigate whether there is a significant difference in the incidence of placenta previa depending on the degree of surgical completion of endometriosis before pregnancy.

Methods This case-control study included 2781 deliveries at the Hirosaki University Hospital between January 2008 and December 2019. The deliveries were divided into a case group with a history of endometriosis ($n=133$) and a control group without endometriosis ($n=2648$). Perinatal outcomes and complications were compared between the case and control groups using a t-test and Fisher's exact test. Multiple logistic regression models were used to identify the risk factors for placenta previa. Additionally, we examined whether the degree of surgical completion of endometriosis before pregnancy was associated with the risk of placenta previa.

Results Patients with a history of endometriosis had a significantly higher risk of placenta previa (crude odds ratio, 2.66; 95% confidence interval, 1.37–4.83). Multiple logistic regression analysis showed that a history of endometriosis was a significant risk factor for placenta previa (adjusted odds ratio, 2.30; 95% confidence interval, 1.22–4.32). In addition, among patients with revised American Society for Reproductive Medicine stage III–IV endometriosis, the incidence of placenta previa was significantly lower in patients who underwent complete surgery (3/51 patients, 5.9%) than in those who did not (3/9 patients, 33.3%) ($p=0.038$).

Conclusions A history of endometriosis is an independent risk factor for placenta previa. Given the limitations of this study, further research is needed to determine the impact of endometriosis surgery on perinatal complications.

Keywords Endometriosis, Placenta previa, Perinatal outcomes, Perinatal complications

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Background

Endometriosis is characterized by the presence of endometrial glands and stromal elements at extrauterine sites. Its clinical manifestations include dysmenorrhea, chronic pelvic pain, and infertility [1–3].

Recently, the number of pregnancies in women with endometriosis has increased owing to the widespread use of assisted reproductive technologies (ARTs). However, several systematic reviews have reported that a history of endometriosis increases the risk of perinatal complications, such as placenta previa and preterm delivery [4–11], and evidence is accumulating. Moreover, more severe endometriosis is associated with a higher risk of perinatal complications [7, 12].

It is unknown whether pre-pregnancy treatment for endometriosis reduces perinatal complications. In a PubMed search, only one systematic review reported obstetric outcomes after surgical treatment of endometriosis [13]. This review included three studies. The first study reported that women who underwent surgery for endometriosis before pregnancy had a significantly higher risk of perinatal complications, such as placenta previa and postpartum hemorrhage, than those who did not [14]. However, the second study found no significant difference in the risk of placenta previa between women who underwent surgery for endometriosis before pregnancy and those who did not, perhaps because of the small sample size [15]. The third study found no significant differences in cesarean section rates, neonatal outcomes, or maternal outcomes between those who underwent surgery for endometriosis before pregnancy and those who did not among women with colorectal endometriosis [16]. These studies were heterogeneous in terms of design, group definitions, and outcome measures. Therefore, their results cannot be generalized. To determine whether the surgical resection of endometriotic lesions decreases the risk of perinatal complications, a comparison between women with similar endometriosis severity and different surgical completion rates is needed.

Thus, in this study, we aimed to clarify the association between endometriosis and perinatal complications and to investigate whether there is a significant difference in the incidence of these complications depending on the degree of surgical completion of endometriosis.

Methods

Aim, design, and setting

We aimed to clarify the association between endometriosis and perinatal complications and investigate whether there is a significant difference in the incidence of these complications depending on the degree of surgical completion of endometriosis. We retrospectively identified all deliveries at Hirosaki University Hospital between January 2008 and December 2019 using electronic medical records.

Study population

The exclusion criteria were multiple pregnancies or deliveries at <22 gestational weeks; 2938 deliveries were identified, of which 157 were excluded because they met the exclusion criteria. The deliveries were divided into two groups: a case group with a history of endometriosis (n=133) and a control group without endometriosis (n=2648). The diagnosis of endometriosis was based on histopathological findings from surgical resection, imaging findings from ultrasonography or magnetic resonance imaging, or endometriotic lesions visually confirmed by intraperitoneal observation. Using the revised American Society for Reproductive Medicine (rASRM) classification, 95 deliveries in patients who underwent surgery for endometriosis were classified based on the severity of endometriosis. The rASRM classification is used worldwide as a standard for assessing the severity of endometriosis [17]. Sixty deliveries were classified as rASRM stages III–IV, nine were classified as rASRM stages I–II, and 26 were unclassifiable owing to insufficient data. Endometriosis surgery includes the enucleation of endometriotic cysts and debridement of adhesions. We reviewed surgical records and videos to assess the degree of surgical completion in patients with rASRM stages III–IV, who are considered to be at high risk for perinatal complications. Our focus was on whether the Douglas fossa adhesions were dissected, as it has been reported that patients with rectovaginal endometriosis have a higher risk of placenta previa than those with endometriotic lesions at other sites [18]. Although there is no consensus on the definition of complete surgery for endometriosis, in this study, complete surgery was defined as the complete dissection of Douglas fossa adhesions and complete excision of pelvic endometriotic lesions. Fifty-one deliveries were classified into the complete surgery group, and nine deliveries were classified into the non-complete surgery group. Figure 1 presents a flowchart of the sample collection criteria.

Perinatal complications

We compared the following perinatal complications: placenta previa, preterm delivery (<37 gestational weeks), hypertensive pregnancy disorders, gestational diabetes mellitus, and placental abruption.

Ethical considerations

The requirement for informed consent was waived because of data anonymity. This study was approved by the Institutional Review Board of the Hirosaki University.

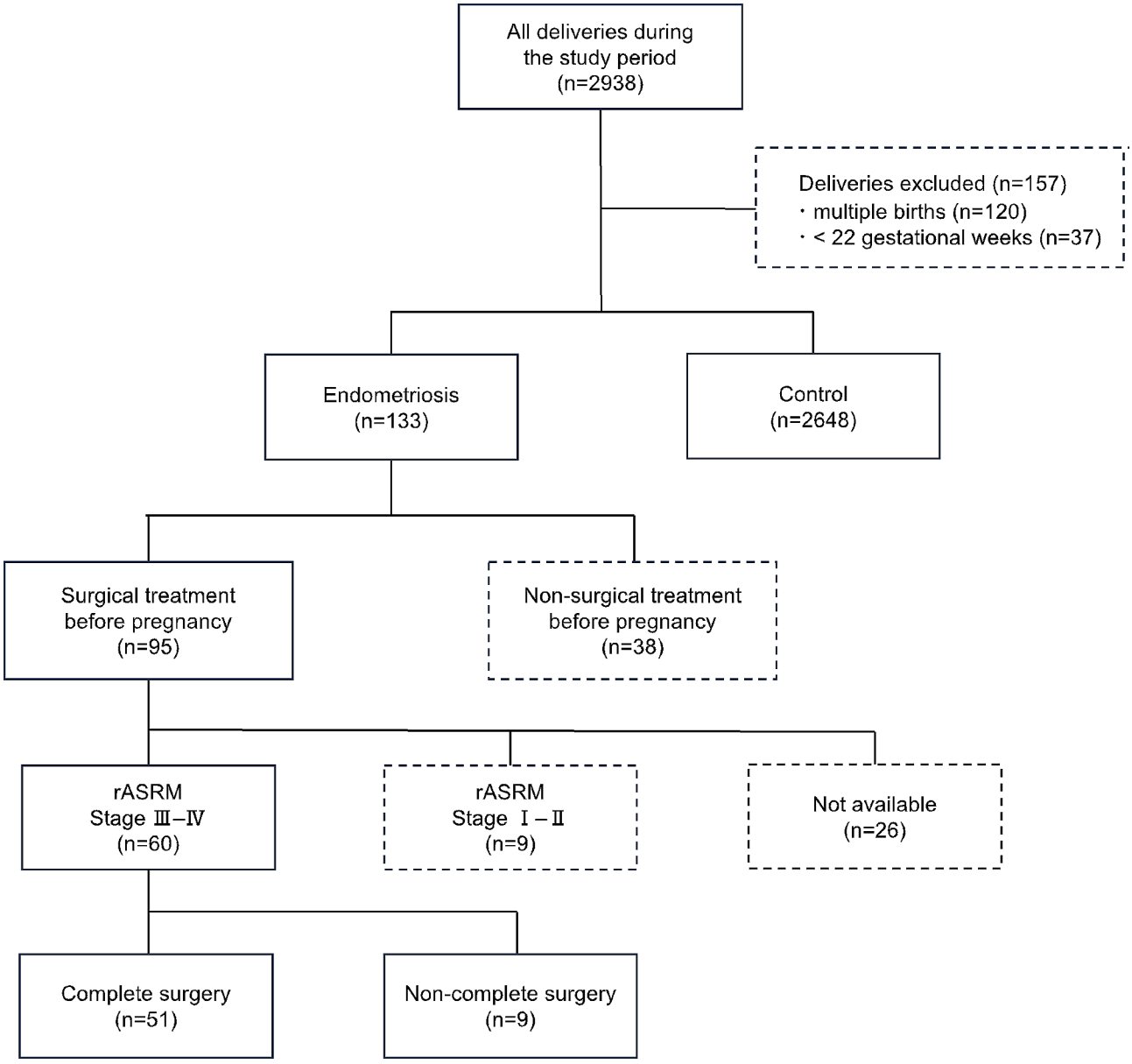

Fig. 1 Flowchart of the sample criteria. rASRM, revised American society for reproductive medicine

Statistical analysis

We used the t-test to compare the averages of continuous variables and Fisher's exact test to compare the proportions of categorical variables between the groups. Multiple logistic regression models were used to identify the risk factors for placenta previa. Based on existing findings, gestational age, number of previous deliveries, ART, previous intrauterine operations, and history of endometriosis were included in the multivariate model [19, 20]. We also included pre-pregnancy body mass index, which was suspected to be associated with the risk of placenta previa in univariate analyses. Intrauterine surgery includes hysteroscopic surgery and uterine curettage. Patients who delivered more than once during the study period were included in the statistical analysis. All data were analyzed using the EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [21]. $P<0.05$ was considered statistically significant.

Results

The patient characteristics in each group are presented in Table 1. Patients with a history of endometriosis were older and had a higher proportion of primiparity, infertility treatments, and ART pregnancies.

Table 2 presents the perinatal outcomes of each group. Patients with a history of endometriosis were significantly more likely to have a cesarean section ($p<0.001$) and had more blood loss at the time of the cesarean

Table 1 Patient characteristics

	Endometriosis (n=133)	Control (n=2648)	P-value
Age (years)	34.23 ± 4.33	32.64 ± 5.32	<0.001*
Pre-Pregnancy BMI (kg/m^2)	21.59 ± 3.25	22.13 ± 4.23	0.15
Primipara	89 (66.9)	1368 (51.6)	<0.001*
Intrauterine operation[a]	33 (24.8)	550 (20.8)	0.28
Infertility treatment	66 (49.6)	537 (20.3)	<0.001*
ART	49 (36.8)	321 (12.1)	<0.001*

Data are presented as mean ± standard deviation or n (%).

BMI, body mass index, ART, assisted reproductive technology.

[a]Intrauterine operation includes hysteroscopic surgery and uterine curettage.

*Statistically significant.

Table 2 Perinatal outcomes

	Endometriosis (n=133)	Control (n=2648)	p-value
Maternal			
Delivery route			
Vaginal delivery	72 (54.1)	2010 (75.9)	<0.001*
Caesarean section	61 (45.9)	638 (24.1)	
Blood loss (g)			
Vaginal delivery	346.31 ± 225.70	347.89 ± 377.17	0.97
Caesarean section	1300.41 ± 682.32	1102.73 ± 675.36	0.029*
Neonatal			
Still birth	1 (0.8)	20 (0.8)	1.0
Neonatal death	0 (0.0)	14 (0.5)	1.0
Weight (g)	2957.26 ± 467.69	2986.35 ± 493.32	0.51
1-minute Apgar score	7.89 ± 1.51	8.08 ± 1.45	0.13
5-minute Apgar score	8.83 ± 1.02	8.83 ± 1.23	0.93

Data are presented as mean ± standard deviation or n (%).

*Statistically significant.

section than controls (p=0.029). The neonatal outcomes were not significantly different between the groups.

The risk of perinatal complications in each group is presented in Table 3. Patients with a history of endometriosis had a significantly higher risk of placenta previa (crude OR, 2.66; 95%CI, 1.37–4.83) and a significantly lower risk of gestational diabetes mellitus (crude OR, 0.37; 95%CI, 0.14–0.80). The preterm birth rates were not significantly different between the groups.

In a multiple logistic regression analysis conducted to examine risk factors for placenta previa, a history of endometriosis was identified as a significant risk factor for placenta previa (adjusted OR, 2.30; 95%CI, 1.22–4.32) (Table 4).

In addition, among patients with rASRM stage III–IV endometriosis, those who underwent complete surgery for endometriosis had a lower rate of placenta previa (3/51 patients, 5.9%) than those who underwent incomplete surgery (3/9 patients, 33.3%) (p=0.038) (Fig. 2). In the complete surgery group, four had recurrent endometriosis on ultrasonography during pregnancy; however, none of them developed placenta previa. Most patients in the incomplete surgery group did not have a complete release of Douglas fossa adhesions.

Table 3 Perinatal complications

	Endometriosis (n=133)	Control (n=2648)	Crude OR (95% CI)	p-value
Preterm birth (<37 weeks)	7 (5.3)	188 (7.1)	0.73 (0.28–1.57)	0.60
Hypertensive Disorders of Pregnancy	7 (5.3)	164 (6.2)	0.84 (0.33–1.83)	0.85
Gestational Diabetes Mellitus	7 (5.3)	345 (13.0)	0.37 (0.14–0.80)	0.0070*
Placenta abruption	0	20 (0.8)	0.00 (0.00–4.05)	0.62
Placenta previa	14 (10.5)	112 (4.2)	2.66 (1.37–4.83)	0.0023*

OR, odds ratio, CI, confidence interval.
Data are presented as n (%).
*Statistically significant.

Table 4 Multivariate analysis for identifying risk factors for placenta previa

	Adjusted OR[b]	95% CI	p-value
Age (years)	1.02	0.98–1.06	0.39
Pre-Pregnancy BMI (kg/m^2)	0.96	0.91–1.01	0.13
Previous parity (times)	1.11	0.88–1.38	0.38
ART	1.65	0.99–2.76	0.054
Intrauterine operation[a]	0.96	0.61–1.52	0.86
Endometriosis	2.30	1.22–4.32	0.0098*

BMI, body mass index; ART, assisted reproductive technology; OR, odds ratio, CI, confidence interval.
[a]Intrauterine operation includes hysteroscopic surgery and uterine curettage.
[b]Adjusted for age, pre-pregnancy BMI, previous parity, ART, intrauterine operation, and history of endometriosis.
*Statistically significant.

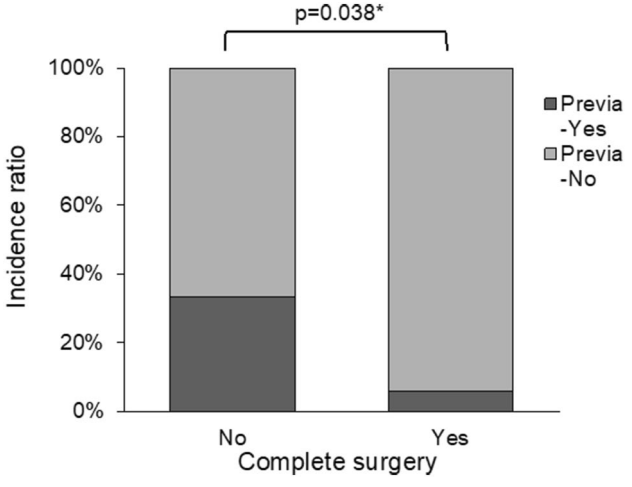

Fig. 2 Incidence ratio of placenta previa with and without complete surgery. Fisher's exact test was used to compare the incidence of placenta previa. *Statistically significant

Discussion

Our findings indicate that a history of endometriosis is an independent risk factor for placenta previa. Furthermore, among patients with rASRM stage III–IV endometriosis, those who underwent complete surgery had a lower incidence of placenta previa than those who did not.

Previous meta-analyses have shown that a history of endometriosis increases the risk of placenta previa, as demonstrated in the present study [4–8]. A recent comprehensive synthesis of systematic reviews and meta-analyses reported that the risk of placenta previa consistently and robustly stood out among various perinatal complications associated with endometriosis [22]. Notably, placenta previa incidence in the endometriosis group was 10.5% in our study, which was considerably higher than that in the general population (0.6–1.1%) [23, 24]. However, contrary to those of previous studies, our results showed that a history of endometriosis did not increase the risk of preterm delivery [9–11] and gestational hypertension [5, 10, 25]. In addition, the incidence of gestational diabetes was significantly lower in the endometriosis group than that observed in previous studies [26, 27]. There are two possible explanations for this discrepancy. First, our hospital mainly deals with high-risk pregnancies; therefore, the proportion of patients with perinatal complications in the control group was higher than that in the general population. The

second reason is the small sample size of patients with endometriosis.

Recently, the association between the severity of endometriosis and the risk of developing placenta previa has become clearer. One meta-analysis reported an increased risk of placenta previa in patients with severe endometriosis, such as deep infiltrating endometriosis (DIE) or rASRM stages III–IV, but not in those without DIE or in those with rASRM stages I–II, compared to those with no history of endometriosis [7]. A retrospective cohort study compared placenta previa incidence based on the site of endometriosis and found that the incidence of endometriosis was significantly higher in women with rectovaginal lesions than in those with endometriosis at other sites [18]. Therefore, the present study sought to determine whether the degree of surgical completion of endometriosis affects the risk of placenta previa in patients with rASRM stage III–IV endometriosis, who are presumed to be at high risk for placenta previa.

Few studies have examined the association between pre-pregnancy surgery for endometriosis and perinatal complications. In a study, women with residual postoperative DIE lesions had a higher risk of placenta previa than those without a history of endometriosis [28]. Another study found an increased risk of placenta previa in women with no history of endometriosis, even when DIE was completely resected before pregnancy [16]. These results suggest that severe endometriosis with DIE may cause irreversible uterine changes. However, previous studies have included patients with no history of endometriosis as controls and have not evaluated whether surgery reduces the risk of placenta previa in patients with endometriosis. To the best of our knowledge, this is the first study to examine whether the degree of surgical completion of endometriosis affects the risk of placenta previa in patients with severe endometriosis. Our results showed that among patients with rASRM stage III–IV endometriosis, those who underwent complete surgery had a lower incidence of placenta previa (3/51 patients, 5.9%) than those who underwent incomplete surgery (3/9 patients, 33.3%) ($p=0.038$). However, the small sample size and variability in surgical methods among institutions and surgeons make it difficult to generalize these findings.

The detailed mechanism by which endometriosis increases the risk of placenta previa remains unknown. However, it is speculated that endometrial molecular abnormalities [29] and changes in uterine contractions observed in women with endometriosis may affect the implantation site of the embryo and increase the risk of placenta previa [30]. Future clarification of the underlying mechanisms by which endometriosis increases the risk of placenta previa may reveal whether pre-pregnancy surgery reduces the risk of endometriosis-related perinatal complications.

This study had some limitations. First, this was a single-center, case-control study. Therefore, selection and information biases may have influenced the results. Additionally, there were missing data concerning patients who underwent surgery for endometriosis at other hospitals, which reduced the amount of data used in the analysis. Therefore, the test power may have been insufficient to investigate the effects of pre-pregnancy surgery on endometriosis. Second, the control group did not undergo laparoscopy; only imaging tests confirmed the absence of endometriosis. Laparoscopy is the most reliable method for diagnosing endometriosis, and imaging alone may underestimate the impact of endometriosis. Third, the effects of adenomyosis were not considered. Diagnosing adenomyosis through imaging is challenging due to the lack of fixed diagnostic criteria. Evaluating mild adenomyosis was particularly difficult using ultrasonography alone, as most patients in the control group did not undergo magnetic resonance imaging. A recent review examining the impact of endometriosis and adenomyosis on pregnancy outcomes suggested that adenomyosis is a significant confounder of pregnancy outcomes and that the impact on the same adverse obstetric outcome may be greater for adenomyosis than for endometriosis [22]. Since endometriosis and adenomyosis often coexist, it is possible that the adverse pregnancy outcomes attributed to endometriosis in this study were actually influenced by the presence of adenomyosis.

Conclusions

Our study revealed that a history of endometriosis is an independent risk factor for placenta previa. Given the limitations of this study, further research is needed to determine the impact of endometriosis surgery on perinatal complications.

Abbreviations

ART	Assisted reproductive technology
DIE	Deep infiltrating endometriosis
rASRM	Revised American Society for Reproductive Medicine

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Author contributions

SU: Formal Analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing. RF: Methodology, Data curation, and Project administration. MY: Investigation, Funding acquisition. AA: Funding acquisition. KI: Formal Analysis. MY: Writing – review & editing. YY: Supervision. All authors read and approved the final manuscript.

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Data availability
The datasets analyzed during this study are not publicly available for ethical reasons but can be obtained from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The requirement for informed consent was waived because the data were anonymized. This study was approved by the Institutional Review Board of Hirosaki University (Reference 2022-089).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. World Health Organ Classif Tumours. Editorial board, ed. Female genital tumours. Lyon: World Health Organization; 2020.
2. Saunders PTK, Horne AW. Endometriosis: etiology, pathobiology, and therapeutic prospects. Cell. 2021;184:2807–24.
3. Smolarz B, Szyłło K, Romanowicz H. Endometriosis: epidemiology, classification, pathogenesis, treatment and genetics (review of literature). Int J Mol Sci. 2021;22:10554.
4. Jeon H, Min J, Kim DK, Seo H, Kim S, Kim YS. Women with endometriosis, especially those who conceived with assisted reproductive technology, have increased risk of placenta previa: meta-analyses. J Korean Med Sci. 2018;33:e234.
5. Horton J, Sterrenburg M, Lane S, Maheshwari A, Li TC, Cheong Y. Reproductive, obstetric, and perinatal outcomes of women with adenomyosis and endometriosis: a systematic review and meta-analysis. Hum Reprod Update. 2019;25:592–632.
6. Matsuzaki S, Ueda Y, Nagase Y, Matsuzaki S, Kakuda M, Kakuda S, et al. Placenta accreta spectrum disorder complicated with endometriosis: systematic review and meta-analysis. Biomedicines. 2022;10:390.
7. Matsuzaki S, Nagase Y, Ueda Y, Kakuda M, Maeda M, Matsuzaki S, et al. Placenta previa complicated with endometriosis: contemporary clinical management, molecular mechanisms, and future research opportunities. Biomedicines. 2021;9:1536.
8. Qu H, Du Y, Yu Y, Wang M, Han T, Yan L. The effect of endometriosis on IVF/ICSI and perinatal outcome: a systematic review and meta-analysis. J Gynecol Obstet Hum Reprod. 2022;51:102446.
9. Huang Y, Zhao X, Chen Y, Wang J, Zheng W, Cao L. Miscarriage on endometriosis and adenomyosis in women by assisted reproductive technology or with spontaneous conception: a systematic review and meta-analysis. BioMed Res Int. 2020;2020:4381346.
10. Wang JQ, Zhang JM, Qian B. Adverse pregnancy outcomes for women with endometriosis: a systematic review and meta-analysis. Ginekol Pol. 2021.
11. Bonuccelli GA, Negrini R, da Silva Ferreira RD. Premature birth in women with endometriosis: a systematic review and meta-analysis. Reprod Sci. 2022;29:250–9.
12. Fujii T, Wada-Hiraike O, Nagamatsu T, Harada M, Hirata T, Koga K, et al. Assisted reproductive technology pregnancy complications are significantly associated with endometriosis severity before conception: a retrospective cohort study. Reprod Biol Endocrinol. 2016;14:73.
13. Mooney SS, Ross V, Stern C, Rogers PAW, Healey M. Obstetric outcome after surgical treatment of endometriosis: a review of the literature. Front Reprod Health. 2021;3:750750.
14. Berlac JF, Hartwell D, Skovlund CW, Langhoff-Roos J, Lidegaard Ø. Endometriosis increases the risk of obstetrical and neonatal complications. Acta Obstet Gynecol Scand. 2017;96:751–60.
15. Miura M, Ushida T, Imai K, Wang J, Moriyama Y, Nakano-Kobayashi T, et al. Adverse effects of endometriosis on pregnancy: a case-control study. BMC Pregnancy Childbirth. 2019;19:373.
16. Nirgianakis K, Gasparri ML, Radan AP, Villiger A, McKinnon B, Mosimann B, et al. Obstetric complications after laparoscopic excision of posterior deep infiltrating endometriosis: a case-control study. Fertil Steril. 2018;110:459–66.
17. American Society for Reproductive Medicine. Revised American Society for Reproductive Medicine classification of endometriosis: 1996. Fertil Steril. 1997;67:817–21.
18. Vercellini P, Parazzini F, Pietropaolo G, Cipriani S, Frattaruolo MP, Fedele L. Pregnancy outcome in women with peritoneal, ovarian and rectovaginal endometriosis: a retrospective cohort study. BJOG. 2012;119:1538–43.
19. Jenabi E, Salimi Z, Bashirian S, Khazaei S, Ayubi E. The risk factors associated with placenta previa: an umbrella review. Placenta. 2022;117:21–7.
20. Oyelese Y, Smulian JC. Placenta previa, placenta accreta, and vasa previa. Obstet Gynecol. 2006;107:927–41.
21. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transpl. 2013;48:452–8.
22. Vercellini P, Viganò P, Bandini V, Buggio L, Berlanda N, Somigliana E. Association of endometriosis and adenomyosis with pregnancy and infertility. Fertil Steril. 2023;119:727–40.
23. Harada T, Taniguchi F, Onishi K, Kurozawa Y, Hayashi K, Harada T, et al. Obstetrical complications in women with endometriosis: a cohort study in Japan. PLoS ONE. 2016;11:e0168476.
24. Healy DL, Breheny S, Halliday J, Jaques A, Rushford D, Garrett C, et al. Prevalence and risk factors for obstetric haemorrhage in 6730 singleton births after assisted reproductive technology in Victoria Australia. Hum Reprod. 2010;25:265–74.
25. Breintoft K, Pinnerup R, Henriksen TB, Rytter D, Uldbjerg N, Forman A, et al. Endometriosis and risk of adverse pregnancy outcome: a systematic review and meta-analysis. J Clin Med. 2021;10:667.
26. Pérez-López FR, Martínez-Domínguez SJ, Viñas A, Pérez-Tambo R, Lafita A, Lajusticia H, et al. Endometriosis and gestational diabetes mellitus risk: a systematic review and meta-analysis. Gynecol Endocrinol. 2018;34:363–9.
27. Lalani S, Choudhry AJ, Firth B, Bacal V, Walker M, Wen SW, et al. Endometriosis and adverse maternal, fetal and neonatal outcomes, a systematic review and meta-analysis. Hum Reprod. 2018;33:1854–65.
28. Exacoustos C, Lauriola I, Lazzeri L, De Felice G, Zupi E. Complications during pregnancy and delivery in women with untreated rectovaginal deep infiltrating endometriosis. Fertil Steril. 2016;106:1129–e11351.
29. Boucher A, Brichant G, Gridelet V, Nisolle M, Ravet S, Timmermans M, et al. Implantation failure in endometriosis patients: etiopathogenesis. J Clin Med. 2022;11:5366.
30. Leyendecker G, Kunz G, Herbertz M, Beil D, Huppert P, Mall G, et al. Uterine peristaltic activity and the development of endometriosis. Ann N Y Acad Sci. 2004;1034:338–55.

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