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Effects of endometriosis on pregnancy outcomes in Fujian province

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Abstract. – OBJECTIVE: Endometriosis is a common gynecological disease, affecting 5 to 10% of women of childbearing age. We analyzed pregnancy complications and neonatal outcomes of patients with pregnancies complicated with endometriosis. The aim of the study was to explore the effects of endometriosis on pregnancy and to evaluate the potential pregnancy risks associated with this disease.

PATIENTS AND METHODS: The retrospective study included 3,809 parturients who were routinely examined, hospitalized and underwent cesarean section delivery in Fujian Maternal and Child Health Hospital from January 2014 to December 2020. Among them, 1,026 parturients were diagnosed with endometriosis after the cesarean section (endometriosis group), and 2,783 parturients without endometriosis comprised the control group. The endometriosis group was further divided into subgroups according to the severity of the disease: 882 parturients with stage I or II of endometriosis, and 144 parturients with stage III or IV of endometriosis. General data of all patients and medical records of pregnancy complications and neonatal outcomes for each group were collected and retrospectively analyzed.

RESULTS: There were no statistically significant differences in the age, gestational age, gestation, and parity times between all groups ($p>0.05$). The incidence of preeclampsia and placenta previa in the endometriosis group was higher than that in the control group ($p<0.05$). There was no significant difference in rates of other pregnancy complications, such as chronic hypertension with pregnancy, preeclampsia with chronic hypertension, hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome, gestational diabetes mellitus (GDM), pregestational diabetes mellitus (PGDM), intrahepatic cholestasis of pregnancy (ICP), premature rupture of membranes or placental abruption between the two groups. The incidence of placenta previa in the group of patients with stage III/IV endometriosis was higher than in patients with stage I/II endometriosis ($p<0.05$). However, there was no significant difference in the incidence of other pregnancy complications. The amount of postpartum hemorrhage (1,000-1,500 ml) in the endometriosis group was greater than that in the control group, and the difference was statistically significant ($p<0.05$). However, there was no significant difference in the incidence of postpartum hemorrhage in patients with pregnancies complicated with endometriosis at different stages.

CONCLUSIONS: In pregnant women, endometriosis is associated with an increased incidence of placenta previa that correlates with the severity of the disease. Pregnant women with endometriosis have higher rates of preeclampsia and postpartum hemorrhage, compared to women without endometriosis

Key Words:
Endometriosis, Pregnancy outcomes, Preeclampsia, Placenta previa, Postpartum hemorrhage.

Introduction

Endometriosis affects between 5 and 10% of all women of childbearing age. It is characterized by the presence and growth of endometrial glands and stroma outside the uterine cavity that undergoes periodic proliferation. The most common location of endometriosis is the pelvic cavity, although some lesions may be located outside the pelvic cavity. Endometriosis lesions are most frequently found in the rectal, uterine depression, but can also involve the uterosacral

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ligament, posterior vaginal wall, and anterior rectal wall. In severe cases, there may even be ureteral involvement[1]. Clinical manifestations of endometriosis include abnormal bowel movements, intestinal dysfunction, dyspareunia, lower abdominal pain, and infertility. Surgical removal of the lesion is a common treatment option that not only reduces the pain but also significantly improves the quality of life. Endometriosis occurs in nearly 50% of infertile women, and 30-40% of women diagnosed with endometriosis report fertility problems[2,3]. Many of these patients choose to conceive through assisted reproductive technologies (ART)[4]. However, it is important to determine whether women with endometriosis can achieve a good pregnancy and perinatal outcome after successful conception[5]. Current research into the treatment of endometriosis predominantly focuses on the improvement of fertility and symptoms. There have been few reports of pregnancy outcomes in women with endometriosis. Previous studies[6,7] have generally reported that pregnancy plays an active role in the treatment of endometriosis and associated pelvic pain, but they mostly ignored the potential negative effects of the disease itself on pregnancy. Although pregnancy complications may vary depending on the type of endometriosis, it increases the overall risk of spontaneous abortion, intrauterine growth restriction, pre-eclampsia, and antenatal hemorrhage, and is associated with a higher risk of delivery by cesarean section. Persistent endometriotic lesions may also cause serious unexpected complications during pregnancy and childbirth[8-12]. Bashir et al[13] reported a case of serious complications during pregnancy that caused massive gastrointestinal bleeding arising from the implantation of decidual tissue in the terminal ileum and colon. Nishikawa et al[14] reported a case of intestinal perforation caused by endometriotic lesions invading the intestine. Therefore, establishing a pregnancy and childbirth risk prediction model based on the medical histories of patients with endometriosis may be of great help to clinicians and will allow them to prevent and manage any complications in a timely manner to avoid potential adverse maternal and neonatal outcomes.

Recent studies demonstrated that inflammatory response plays a crucial role in the pathogenesis of endometriosis[15]. While pregnancy-related changes in immune regulation, in addition to fluctuations in hormones and metabolism, and increased angiogenesis, cause the ectopic endometrium to shrink in response to a lack of estrogen support, studies[12] show that endocrine environment of pregnancy does not prevent the progression of endometriosis. Studies[13-14, 16] have also suggested that endometriosis may negatively affect pregnancy, increasing the risks of pre-eclampsia, intrauterine growth restriction, abnormal placental position, pre- and postpartum hemorrhage, as well as increased risk of delivery by cesarean section.

However, some of these studies[16] included a small number of women and failed to consider potential confounding factors that negatively affect pregnancy, such as twin pregnancies. In the present study, we limited the research subjects to singleton pregnancies to avoid the confounding effects of twin pregnancies. Our research examines the impact of endometriosis on pregnancy outcomes and the possible mechanisms involved.

Patients and Methods

Patients and Grouping

This retrospective study included 4,580 women with singleton pregnancies carried to ≥24 completed weeks of gestation who were treated at the Fujian Provincial Maternity and Children's Hospital, China, Fujian, Fuzhou, between January 2014 and December 2020. Of them, 771 women were excluded due to comorbidities, learning difficulties, serious mental illness, or major fetal abnormality identified at the time of screening. Finally, 3,809 women were included and divided into two groups based on the diagnosis of endometriosis. The study group included 1,026 women with endometriosis, and the control group included 2,783 women without endometriosis. Figure 1 shows a detailed flow chart of the study. The Ethics Committee of Fujian Maternal and Child Health Hospital approved the study (No. 2023-Y-057, Date: June 13th, 2023).

Inclusion and Exclusion Criteria

The inclusion criteria for this study were as follows: age ≥18 years; singleton pregnancy; delivery by cesarean section at our hospital. The exclusion criteria were unconsciousness or severe illness; learning difficulties or serious mental illness; major fetal abnormalities identified at the time of screening; endocrine, autoimmune, or systemic diseases, such as hypertension or

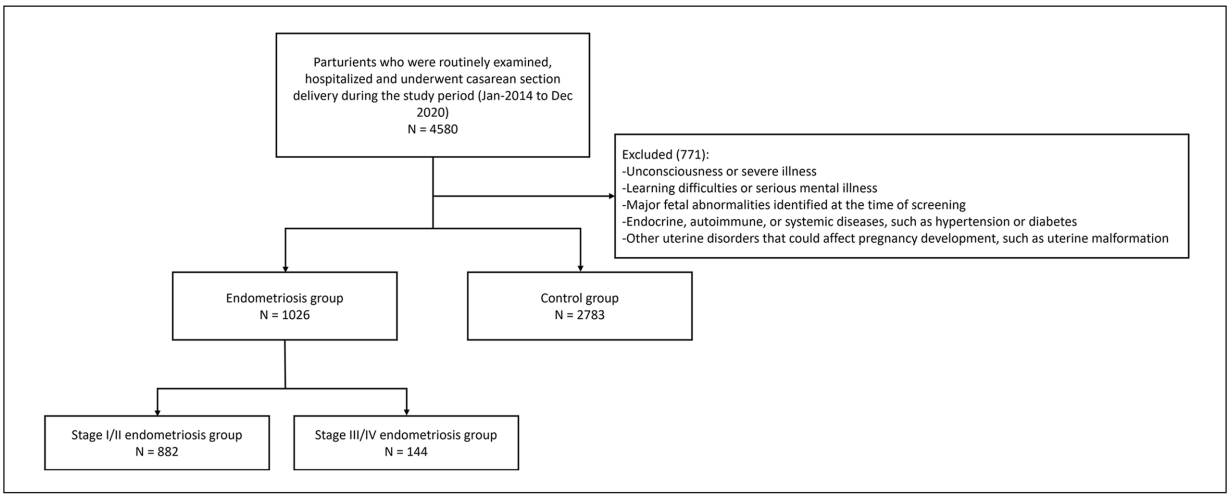

Figure 1. Flow chart of the study.

diabetes; or other uterine disorders that could affect pregnancy development, such as uterine malformation.

Diagnosis of endometriosis was done by laparoscopic examination, and the stage of endometriosis (was determined based on the revised American Society for Reproductive Medicine (rASRM) classification[17]. Stage I indicated mild endometriosis, Stage II-moderate, Stage III-severe and Stage IV- extensive.

Outcome Measurements

We reviewed the records of 3,809 women who delivered their infants during the study period and obtained the following information: pregnancy and delivery characteristics, including gestational age (years; determined from the fetal crow-rump length), gestational age (weeks), gravidity, parity, neonatal weight, placental weight, and amount of bleeding; mode of conception, including natural conception and *via* ART; pregnancy outcomes and maternal complications, including hypertension in pregnancy, hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome, premature rupture of membranes, postpartum hemorrhage, gestational diabetes mellitus (GDM), pregestational diabetes mellitus (PGDM), placental abruption, intrahepatic cholestasis of pregnancy (ICP), placenta previa, premature birth, small-for-gestational-age fetal status (SGA), and APGAR scores at 1 min and 5 min.

A 75-g oral glucose tolerance test (OGTT) was performed between the 24th and 28th weeks of gestation in all pregnant women who had not been diagnosed previously with diabetes. The diagnostic criteria for GDM were based on the guidelines of the National Health and Family Planning Commission of the People's Republic of China. When plasma glucose levels after the 75-g OGTT met or exceeded 5.1 mmol/L at 0 h; 10.0 mmol/L at 1 h; 8.5 mmol/L at 2 h, women were diagnosed with GDM. 'Hypertension in pregnancy' was defined as a systolic blood pressure of ≥140 mmHg or a diastolic blood pressure of ≥90 mmHg. When measured with semiquantitative urine dipsticks, proteinuria of at least 1+ in the presence of hypertension, with no evidence of urinary tract infection, was considered significant. Hypertensive disorders of pregnancy were classified as gestational hypertension, chronic hypertension, chronic hypertension with preeclampsia, pre-eclampsia, or eclampsia. A diagnosis of preterm rupture of membranes was confirmed with well-established clinical and/or biological diagnostic procedures: the visualization of amniotic fluid passing from the cervical canal and pooling in the vagina; a basic pH test of the vaginal fluid; or arborization (ferning) of the dried vaginal fluid, identified with microscopy. The diagnosis of ICP was based on new-onset pruritus, with a total bile acid level >10 μmol/L in the absence of other liver diseases. SGA was defined as a neonatal birthweight below the 10th percentile for gestational age. HELLP syndrome was defined as intravascular hemolysis (serum lactate dehydrogenase >600 IU/L; bilirubin >1.2 mg/dL; presence of schistocytes in the peripheral blood), elevated liver enzymes (serum alanine aminotransferase >40 U/L or aspartate aminotransferase >70 IU/L), and thrombocytope-

nia (platelet count <100,000/mm^3). The diagnosis of placental abruption was based on clinical findings of abdominal pain, vaginal bleeding, uterine contractions, fetal distress, and abnormal vital signs. Placenta previa was defined as a placenta completely or partially covering the internal cervical os, based on transvaginal ultrasonography performed during the third trimester when the patient had an empty bladder. We excluded women with multiple gestations or a gestational age <24 weeks.

Statistical Analysis

SPSS 26.0 (IBM Corp., Armonk, NY, USA) was used for all statistical analyses. Continuous data (e.g., age and operating time) are presented as the mean±standard deviation (SD) and were analyzed with an independent-samples *t*-test or a nonparametric test (Kruskal-Wallis test). Dichotomous data (e.g., sex) are presented as percentages and were compared between the two groups with the χ^2 test or a nonparametric test (Fisher's exact test). Significance was set at $p<0.05$. In the outcome analysis, relative risks and differences in absolute risk were calculated for dichotomous outcomes, together with their 95% confidence intervals (95% CI), using Fisher's exact test.

Results

Table I and Table II list the comparison of some baseline characteristics between the endometriosis group and the control group and the comparison of baseline characteristics between patients with different degrees of endometriosis. No difference in age, proportion of primiparas, or gestational age was found between the two groups of patients. There was also no difference in age, proportion of primiparas, or gestational age between the stage I/II endometriosis group and the stage III/IV endometriosis group.

Tables III and IV list the incidence of pregnancy-related complications in the endometriosis group and the control group and the incidence of pregnancy complications in patients with different stages of endometriosis. The incidence of preeclampsia and placenta previa in the endometriosis group was significantly higher than that in the control group (Table III; $p<0.05$). There was no significant difference in other pregnancy complications (such as chronic hypertension with pregnancy, preeclampsia with chronic hypertension, HELLP syndrome, GDM, PGDM, ICP, premature rupture of membranes, or placental abruption) onset between both groups (Table III).

Table I. Baseline characteristics of the patients in the endometriosis and the control group.

Baseline characteristics	Endometriosis (%) n = 1026	Control group (%) n = 2783	*p*-value
Maternal age (years, average ± S/D)	31.96 ± 4.38	31.75 ± 4.33	0.169
Gestational age (weeks, average ± S/D)	38.73 ± 2.14	38.73 ± 1.78	0.924
Gravidity	-	-	-
= 1	422 (41.13)	1100 (39.53)	0.370
> 1	604 (58.87)	1683 (60.47)	0.370
Parity	-	-	-
= 0	562 (54.78)	1441 (51.78)	0.100
≥ 1	464 (45.22)	1342 (48.22)	0.100

Table II. Baseline characteristics of patients with different stages of endometriosis.

Baseline characteristics	I or II stage (%) n = 882	III or IV stage (%) n = 144	*p*-value
Maternal age (years, average ± S/D)	31.88 ± 4.34	32.49 ± 4.58	0.119
Gestational age (weeks, average ± S/D)	38.78 ± 2.14	38.46 ± 2.09	0.100
Gravidity	-	-	-
= 1	367 (41.61)	55 (38.19)	0.440
> 1	515 (58.39)	89 (61.81)	0.440
Parity	-	-	-
= 0	485 (54.99)	77 (53.47)	0.735
≥ 1	397 (45.01)	67 (46.53)	0.735

Table III. Gestational complications of the endometriosis and the control group.

Gestational complications	Endometriosis (%) n = 1026	Control group (%) n = 2783	*p*-value
Hypertensive disorders of pregnancy			
Gestational hypertension	19 (1.85)	60 (2.16)	0.559
Preeclampsia	38 (3.70)	61 (2.19)	0.009
Chronic hypertension complicating pregnancy	5 (0.49)	20 (0.72)	0.433
preeclampsia superimposed upon chronic hypertension	3 (0.29)	9 (0.32)	> 0.999
HELLP syndrome	1 (0.10)	4 (0.14)	> 0.999
Gestational diabetes	194 (18.91)	535 (19.22)	0.826
Pre-pregnancy diabetes	2 (0.19)	8 (0.29)	0.890
Intrahepatic cholestasis of pregnancy	11 (1.07)	49 (1.76)	0.130
Premature rupture of membranes	126 (12.28)	358 (12.86)	0.632
placental abruption	19 (1.85)	53 (1.90)	0.916
Placenta previa	65 (6.34)	67 (2.41)	< 0.001
Postpartum hemorrhage	15 (1.46)	9 (0.32)	< 0.001

Table IV. Gestational complications of patients with different stages of endometriosis.

Gestational complications	I or II stage (%) n = 882	III or IV stage (%) n = 144	*p*-value
Hypertensive disorders of pregnancy			
Gestational hypertension	17 (1.93)	2 (1.39)	0.912
Preeclampsia	34 (3.85)	4 (2.78)	0.526
Chronic hypertension complicating pregnancy	3 (0.34)	2 (1.39)	0.303
Preeclampsia superimposed upon chronic hypertension	2 (0.23)	1 (0.69)	0.895
HELLP syndrome	1 (0.11)	0 (0.00)	> 0.999
Gestational diabetes	164 (18.59)	30 (20.83)	0.525
Pre-pregnancy diabetes	2 (0.23)	0 (0.00)	> 0.999
Intrahepatic cholestasis of pregnancy	9 (1.02)	2 (1.39)	> 0.999
Premature rupture of membranes	106 (12.02)	20 (13.89)	0.526
Placental abruption	18 (2.04)	1 (0.69)	0.437
Placenta previa	44 (4.99)	21 (14.58)	< 0.001
Postpartum hemorrhage	12 (1.36)	3 (2.08)	0.768

As shown in Table IV, the incidence of placenta previa in patients with stage III/IV endometriosis was higher than in patients with stage I/II endometriosis ($p<0.05$). However, there was no significant difference in the incidence of other pregnancy complications. Endometriosis affects the internal environment of the uterus and causes embryo colonization disorders, which leads to an increase in the incidence of placenta previa, and the incidence increases with the severity of endometriosis.

Tables V and VI summarize the differences in the incidence of postpartum hemorrhage between the endometriosis group and the control group and the incidence of postpartum hemorrhage in patients with different stages

Table V. Amount of bleeding in the endometriosis and the control groups.

Amount of bleeding (ml)	No (%) of PPH		*p*-value
	Endometriosis (%) n = 1026	Control group (%) n = 2783	
1,000-	11 (1.07)	2 (0.07)	< 0.001
1,500-	4 (0.39)	7 (0.25)	0.715
Total	15 (1.46)	9 (0.32)	< 0.001

PPH = postpartum hemorrhage.

Table VI. Amount of bleeding in patients with different stages of endometriosis.

Amount of bleeding (ml)	No (%) of PPH		p-value
	I or II stage (%) n = 882	III or IV stage (%) n = 144	
1,000-	9 (1.02)	2 (1.39)	> 0.999
1,500-	3 (0.34)	1 (0.69)	0.454
Total	12 (1.36)	3 (2.08)	0.768

PPH = postpartum hemorrhage.

of endometriosis. The amount of postpartum hemorrhage (1,000-1,500 ml) in the endometriosis group was greater than that in the control group ($p<0.05$). However, there is no significant difference in the incidence of postpartum hemorrhage and the amount of postpartum hemorrhage in patients with endometriosis of different stages.

As shown in Tables VII and VIII, no significant differences were found in terms of other related fetal outcome factors, such as birth weight, SGA incidence, preterm birth, or APGAR score.

Discussion

Endometriosis and Placenta Previa

The results of our study showed that endometriosis was associated with the increased incidence of placenta previa that correlated with the severity of the disease (endometriosis stage). A large-scale population survey conducted by Blondel et al[18] in France, showed that 5-10% of the female population have endometriosis or a history of endometriosis surgery and that the incidences of SGA, preterm birth, and placenta

Table VII. Fetal and neonatal outcomes of the endometriosis and the control group.

Fetal and neonatal outcomes	Endometriosis (%) n = 10,262	Control group (%) n = 2,783	p-value
Birth weight (g)			
< 2,500	90 (8.77)	226 (8.12)	0.518
2,500-2,999	226 (22.03)	559 (20.09)	0.189
3,000-3,499	414 (40.35)	1179 (42.36)	0.264
3,500-3,999	229 (22.32)	673 (24.18)	0.230
≥ 4,000	67 (6.95)	146 (5.25)	0.126
Small for gestational age (< 10^{th} percentile)	20 (1.95)	58 (2.08)	0.794
Preterm birth	44 (4.29)	115 (4.13)	0.831
APGAR ≤ 7 at 1 min	12 (1.17)	26 (0.93)	0.517
APGAR ≤ 7 at 5 min	1 (0.10)	3 (0.11)	> 0.999

Table VIII. Fetal and neonatal outcomes in patients with different stages of endometriosis.

Fetal and neonatal outcomes	I or II stage (%) n = 882	III or IV stage (%) n = 144	p-value
Birth weight (g)			
< 2,500	76 (8.62)	14 (9.72)	0.664
2,500-2,999	185 (20.98)	41 (28.47)	0.044
3,000-3,499	361 (40.93)	53 (36.81)	0.350
3,500-3,999	199 (22.56)	30 (20.83)	0.644
≥ 4,000	61 (6.92)	6 (4.17)	0.216
Small for gestational age (< 10^{th} percentile)	18 (2.04)	2 (1.39)	0.842
Preterm birth	39 (4.42)	5 (3.47)	0.602
APGAR ≤ 7 at 1 min	9 (1.02)	3 (2.08)	0.495
APGAR ≤ 7 at 5 min	1 (0.11)	0 (0.00)	> 0.999

previa in this population of patients were 10.8%, 6.0%, and 1.1%, respectively. However, in a retrospective study by Farella et al[19] that included 566 patients with endometriosis who had undergone surgical treatment, the incidences of SGA, preterm birth, and placenta previa in singleton pregnancies were 15.1%, 9.9%, and 1.7%, respectively. These values were somewhat greater than those reported Blondel et al[18], possibly because the study by Farella et al[19] included a high proportion of patients with stage III or IV endometriosis (67%), whereas the French large-scale population survey included a lower proportion of patients with stage III or IV endometriosis. This suggests that the outcome of pregnancy may be related to the stage of endometriosis. Berlac et al[20] reported that the rate of corrected placenta previa in patients with severe endometriosis was approximately twice of that in patients without endometriosis. Studies[5,21,22] demonstrated a link between endometriosis and placenta previa, as abnormal uterine contractions in patients with endometriosis may lead to the atypical implantation of the blastocyst. Additionally, abnormal spiral artery remodeling, inflammation, oxidative stress, and an imbalance in the endometrial angiogenic environment may all cause placental abnormalities. Pelvic adhesions secondary to endometriosis may limit uterine movement and create an inflammatory intrauterine environment. In patients with endometriosis, especially those with rectosigmoid disease, the position of the uterus is fixed and affected by uterine dysplasia or dense pelvic adhesions. Theoretically, this reduces the effectiveness of myometrial contractility. Defects in the process of decidualization and placenta formation cause serious uterine dysfunction during blastocyst implantation, resulting in the abnormal remodeling of the uterine spiral arteries[23]. Uterine dysfunction may be associated with the changes in the myometrial junction area caused by adenomyosis and insufficient myometrial contractility, and may also be related to the local inflammatory response of endometriotic lesions and progesterone resistance[24]. In women with endometriosis, the inflammatory microenvironment may also alter the balance of cytokines and normal maternal-fetal tolerance during pregnancy.

The effects of estrogen excess and the inflammatory nature of endometriosis may lead to a variety of pathophysiological changes in the ectopic endometrium[25]. Specifically, increased levels of inflammatory mediators in patients with endometriosis, activation of oxidative stress pathways, and abnormalities in the uterine junction may alter endometrial decidualization and the transformation of the uterine spiral arteries into uterine placental vessels. These changes subsequently may lead to placental disease and normal embryo implantation. As the disease progresses, the incidence of embryo implantation disorders also increases. The endometrium of women with endometriosis has different histological and molecular characteristics compared to that of unaffected women and is associated with changes in the activation of signaling pathways related to cell proliferation and survival[26]. This ultimately leads to an increase in the incidence of abnormal embryo implantation, such as placenta previa, and the severity of endometriosis correlates with the increased incidence of these conditions.

Endometriosis and Hypertension in Pregnancy

Our study showed that endometriosis was associated with an increased incidence of preeclampsia. The relationships between endometriosis and hypertension in pregnancy and fetal intrauterine growth restriction may be related to the thickening of the myometrial junction due to the invasion of trophoblasts into this layer that is essential for pregnancy[24]. However, until recently, it was unclear whether endometriosis increases the incidence of hypertension-related diseases during pregnancy, such as preeclampsia. In 2009, a study[27] of pregnant patients with endometriosis showed a significantly increased risk of preeclampsia in this group of patients. On the other hand, in an earlier study, Borisova et al[16] showed that the incidence of hypertension and preeclampsia during pregnancy was about 7.5% lower in women with endometriosis than in the control group. A meta-analysis, published in 2017 and including 33 studies, showed an increased risk of gestational hypertension (OR = 1.21 [1.05–1.39]) and preeclampsia (OR= 1.18 [1.01–1.39]) in women with endometriosis[11]. Our results confirm these findings. We reported that the incidence of preeclampsia was significantly higher in the endometriosis group than in the control group.

The pathophysiological mechanisms underlying the elevated incidence of preeclampsia mainly include inflammation and abnormal activation of immune pathways, and epigenetic, and environmental factors[21,22] that may lead to reduced activity of the killing cells. As a result, the ectopic endometrium cannot be effectively removed. Studies[28] have shown that endometriosis is al-

so associated with certain autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus. In patients with preeclampsia, inflammatory cytokine response, oxidative stress, vascular endothelial cell dysfunction, and impaired angiogenesis regulatory imbalance may all lead to hyperactivation of the maternal inflammatory immunity and insufficient uterine helical arteriole recasting[29]. Due to similarities in the pathogenic mechanisms in the inflammatory immune response, patients with endometriosis may be more likely to develop preeclampsia. Nirgianakis et al[30] show that in women with endometriosis, the risk of gestational hypertension during pregnancy was still higher even after laparoscopic excision of posterior deep infiltrating endometriosis. In recent years, studies[31-33] have suggested that epigenetic changes may play a pivotal role in the development of endometriosis. Similar epigenetic changes may occur in endometriosis and preeclampsia, either between the imprinted genes (*CDKN1C, DLX5, GATA3*) or in the DNA methylation profiles *(PTGER2)*[34]. However, epigenetic changes are reversible and very sensitive to environmental changes, so the underlying mechanisms of common genetic changes between endometriosis and eclampsia are still unclear.

Endometriosis and Postpartum Hemorrhage

Our study showed that endometriosis was associated with an increased risk of postpartum hemorrhage of over 1,000 mL compared to women without endometriosis. Postpartum hemorrhage is characterized by blood loss after vaginal delivery exceeding 500 mL or exceeding 1,000 mL during cesarean section within 24 h. It is a serious complication during delivery that seriously threatens the life of the mother. The present study demonstrates that patients with endometriosis have a higher incidence of postpartum hemorrhage exceeding 1,000 mL. These results agree with the previous observations that showed the correlation between the increased risk of postpartum hemorrhage and endometriosis[35]. In our study, the severity of endometriosis did not correlate with the increased rate of postpartum hemorrhage. Higher incidence of postpartum blood loss may be explained by unique pathophysiological mechanisms in patients with endometriosis, including abnormal myometrial contractions and the resulting abnormal blastocyst implantation, pelvic adhesions, as well as abnormal remodeling of the spiral arteries, inflammation, oxidative stress, and an unbalanced endometrial angiogenic environment. Placental factors are among the high-risk factors for postpartum hemorrhage. In patients with endometriosis, the position of the uterus is fixed and abnormal due to dysplasia of the uterus or dense pelvic adhesions, which can theoretically reduce effective myometrial contractility, resulting in postpartum uterine inertia. This, in turn, may affect myometrial contraction and cause increased postpartum bleeding. The expression of vascular endothelial growth factor (VEGF), an important regulator of angiogenesis, is also higher in patients with endometriosis. Similarly, endometriosis is associated with the increased expression of several vascular growth factors and cytokines, including interleukin (IL)-1, IL-6, IL8, epidermal growth factor, insulin-like growth factor, and platelet-derived growth factor in the ectopic intima. This may lead to increased permeability of vascular endothelial cells and may promote the formation of new blood vessels, eventually increasing the amount of postpartum bleeding in patients with endometriosis[36,37].

Endometriosis and Maternal and Neonatal Outcomes

Our study showed no association of endometriosis with diabetes mellitus (GDM), pregestational diabetes mellitus (PGDM), intrahepatic cholestasis of pregnancy (ICP), premature rupture of membranes or placental abruption between the two groups. Our results are different from the results of the meta-analysis by Lalani et al.[11] that showed an increased risk of ICP, diabetes, SGA, NICU admission and stillbirth in women with endometriosis. We may speculate that the discrepancy between our observations and the results of the meta-analysis may be due to the fact that the diagnosis for endometriosis, as well as the selection of control groups was not uniform between the studies, included in the meta-analysis.

Limitations

Our study has some limitations. Previous studies[8-11] on pregnancy comorbidities in patients with endometriosis suffered from both recall bias and reporting errors due to the problems associated with data collection. In this study, we did not conduct a stratified analysis of the types of endometriotic lesions or the presence or absence of adenomyosis. Moreover, the variability in the existing diagnostic criteria for endometriosis, the heterogeneity and the potential confounding factors that were not accounted for (such as the

type of endometriotic lesions, the presence or absence of adenomyosis, the use of assisted reproductive techniques, etc.) weaken the validity of our research results. Similarly designed studies[11] have reported different results, so the pathogenesis of endometriosis requires further research to confirm our findings. The current hotspots of endometriosis research predominantly focus on pregnancy itself, and there are relatively few studies[38] that explore the long-term outcomes of pregnancy in these patients. A more comprehensive understanding of this disease may allow timely prevention and treatment of the related complications and ultimately improve maternal and neonatal outcomes.

Conclusions

In pregnant women, endometriosis is associated with an increased incidence of placenta previa, and the severity of the disease correlates with the rate of this complication. Pregnant women with endometriosis have higher rates of preeclampsia and postpartum hemorrhage, compared to women without endometriosis.

Conflict of Interest
The authors declare that they have no conflict of interests.

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Ethics Approval
The Ethics Committee of Fujian Maternal and Child Health Hospital approved the study (No. 2023-Y-057, Date: June 13th, 2023). All methods were performed according to the Declaration of Helsinki.

Informed Consent
Because of the study's retrospective nature, informed patient consent was waived.

Availability of Data and Materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Authors' Contribution
Conception/Design: SJT and ZZL. Collection and/or assembly of data: SJT, YLZ, JYW, and ZZL. Data analysis and interpretation: SJT, YLZ, JYW, and ZZL. Manuscript writing: SJT and ZZL. All authors have read and approved the final manuscript.

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