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ORIGINAL RESEARCH

Endometriosis Severity and Risk of Preeclampsia: A Combined Mendelian Randomization and Observational Study

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Purpose: Endometriosis has been hypothesized to increase the risk of preeclampsia (PE) and eclampsia, although the exact mechanism of this relationship is not clear. This study aimed to further explore the potential association between endometriosis and PE/eclampsia through Mendelian randomization (MR) and confirm these findings in a retrospective cohort study.

Methods: A two-sample MR study was performed using genetic variants associated with endometriosis from the Finnish database, with outcome data for PE and eclampsia from the UK Biobank. Subgroup analyses were conducted based on endometriosis severity (American society of reproductive Medicine (ASRM) stages I–II and III–IV) and anatomical location (uterus, ovary, deep infiltrating endometriosis). Additionally, a retrospective cohort study was conducted to further assess the association, adjusting for confounding factors such as age, Body Mass Index (BMI), dysmenorrhea, history of uterine surgery, and adenomyosis. Multivariate logistic regression was used to analyze the risk of PE/eclampsia based on endometriosis severity.

Results: MR using the Inverse Variance Weighted method found a meaningful association between advanced endometriosis (ASRM stages III–IV) and PE/eclampsia ($p = 0.008$), while no significant associations were observed for lower stages or endometriosis in the uterus and ovary. In the retrospective cohort, the initial association between the revised American Fertility Society (r-AFS) score and PE/eclampsia (OR: 1.02, 95% CI: 1.01–1.03, $p < 0.001$) weakened after adjusting for confounders. Significant risk factors identified included age (OR: 1.20, 95% CI: 1.10–1.30, $p < 0.001$), dysmenorrhea (OR: 2.72, 95% CI: 1.31–5.76, $p = 0.008$) and adenomyosis showing the strongest association (OR: 9.96, 95% CI: 5.00–20.06, $p < 0.001$).

Conclusion: The findings suggest a potential relationship between advanced endometriosis and the risk of PE/eclampsia. However, other clinical factors such as age, dysmenorrhea, and adenomyosis appear to contribute more significantly to the risk. Further studies are needed to confirm these findings and clarify the underlying mechanisms.

Keywords: endometriosis, preeclampsia, Mendelian randomization, retrospective cohort, adenomyosis, dysmenorrhea

Introduction

Endometriosis is a chronic gynecological condition characterized by the presence of endometrial-like tissue outside the uterine cavity, typically affecting the ovaries, pelvic peritoneum, and other reproductive organs.[1–5] Affecting approximately 10–15% of women of reproductive age, endometriosis is associated with a range of symptoms, including pelvic pain, severe dysmenorrhea, and infertility.[6–8] While extensive research has explored the reproductive consequences of endometriosis, its potential impact on pregnancy outcomes, specifically hypertensive disorders of pregnancy (HDP) such

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as preeclampsia (PE) and gestational hypertension disease (GHD), remains an area of growing interest. HDP represents a significant health concern for pregnant women worldwide, leading to severe maternal and fetal complications.[9–11]

HDP, including GHD and PE, are among the most common complications in pregnancy, affecting around 10% of pregnancies globally.[12–14] Current risk factors for these disorders include maternal age, pre-pregnancy obesity, and certain chronic conditions like polycystic ovarian syndrome (PCOS) and chronic hypertension.[15] Although there has been increasing evidence suggesting that endometriosis may be associated with an elevated risk of hypertensive disorders during pregnancy, the exact mechanisms underlying this association remain unclear.[5] Inflammatory and immunological alterations linked to endometriosis may interfere with placental function, contributing to adverse pregnancy outcomes.[16]

Despite several studies addressing the possible connection between endometriosis and hypertensive disorders, conflicting findings persist. While some studies report a significant association, others suggest no link or even protective effects.[17] This inconsistency may be due to variations in study design, sample sizes, or diagnostic criteria for endometriosis and hypertensive disorders.

Therefore, this study aims to further investigate the relationship between endometriosis and hypertensive disorders in pregnancy using Mendelian randomization (MR) and retrospective cohort analyses to provide more definitive insights into the association between these conditions.

Methods

Study Design and Patients

This study used both MR and a retrospective observational design to investigate the association between endometriosis and PE/eclampsia. In the MR study, genetic data were drawn from the Finnish database for endometriosis and the UK Biobank for PE and eclampsia outcomes. Stratified analyses were conducted based on the anatomical location and severity of endometriosis (American society of reproductive Medicine (ASRM) stages I–II and III–IV).

For the retrospective cohort study, 2142 patients diagnosed with endometriosis via laparoscopic surgery were screened. Patients who were lost to follow-up (n=214), did not plan to conceive or were not pregnant (n=1080), had chronic hypertension (n=11), or experienced miscarriage before 28 weeks of gestation (n=66) were excluded. A total of 753 patients who successfully conceived and delivered after at least 28 weeks of pregnancy were included in the final analysis, including 11 cases of gestational hypertension and 55 cases of PE.

Mendelian Randomization

MR is a method that uses genetic variants as instrumental variables to infer the causality between exposure factors and outcomes in observational studies. In an MR analysis, genetic variants, commonly single nucleotide poly morphisms, are used as instrumental variables for the putative risk factor. The principle of MR refers to Mendel's second law of independent segregation of genetic alleles when DNA is transmitted from parents to offspring at gamete formation.[18]

The etiology of endometriosis is still unclear, but the heritability of the disease is estimated to be around 50%, with approximately 26% attributed to common genetic variations.[19] A study included 17,045 cases and 191,596 controls, identifying 19 unique associations at a genome-wide significance level ($p<5\times10^{-8}$), mapped to 13 loci separated by more than 1Mb, collectively explaining 1.75% of the phenotypic variation of endometriosis.[20]

This study uses a two-sample MR approach to explore the potential relationship between endometriosis and PE/eclampsia. Genetic variants associated with endometriosis were selected from a genome-wide association study (GWAS) of the Finnish cohort as instrumental variables, and summary-level data for PE/eclampsia were sourced from the UK Biobank. This design allowed us to reduce the impact of confounding factors on the relationship between genetic variations and clinical outcomes.

To further assess the impact of the severity and anatomical location of endometriosis on the study results, we conducted subgroup analyses based on the severity of endometriosis (ASRM stages I–II and III–IV) and anatomical sites (uterus, ovaries, deep infiltrating endometriosis (DIE)). The inverse variance weighted (IVW) method was employed as the primary analysis, with MR-Egger and weighted median methods used to assess pleiotropy and robustness.

Surgical Procedure

All patients in the observational cohort underwent laparoscopic surgery, where endometriosis was classified using the revised American Fertility Society (r-AFS) classification. The surgical team, experienced in gynecological laparoscopic procedures, performed excision or ablation of endometriotic lesions based on standard techniques. The surgical intervention was aimed at alleviating symptoms and improving reproductive outcomes.[21]

Diagnosis of Adenomyosis

In our study, the diagnosis of adenomyosis was established through an integrative approach that encompassed clinical assessments, physical examinations and imaging techniques. We particularly use transvaginal ultrasound and magnetic resonance imaging (MRI) to identify unique features associated with adenomyosis. The main diagnostic points of transvaginal ultrasound include: uterine enlargement, asymmetry of anterior and posterior uterine walls, presence of myometrial cysts, heterogeneous myometrium, hyperechoic or hypoechoic linear striation in the myometrium, poorly delineated junctional zone (JZ), and the presence of echogenic striations in the sub-endometrium, as well as subendometrial echogenic nodules.[22] Additionally, on T2-weighted MRI, a hypointense junctional zone can be seen separating the hyperintense endometrium and intermediate-intensity myometrium.[23]

Data Collection

Pre-surgical demographic and clinical data, including age, Body Mass Index (BMI), medical history, and endometriosis severity, were collected. Post-operative follow-up involved tracking pregnancy outcomes, including gestational hypertension and PE, through hospital records. Additional data on potential confounders, such as infertility, dysmenorrhea, history of uterine surgery, and adenomyosis, were also documented.[6]

Statistical Analysis

For the MR analysis, odds ratios (OR) with 95% confidence intervals (CI) were calculated using the IVW method. P-values less than 0.05 were considered statistically meaningful. In the retrospective cohort study, logistic regression models were used to assess the relationship between r-AFS score and PE, with adjustments made for age, BMI, dysmenorrhea, adenomyosis, and history of uterine surgery. Results were expressed as adjusted odds ratios with 95% confidence intervals, and statistical significance was set at $p < 0.05$. All analyses were conducted using the MR package in R (version 4.3.1).

Results

The Mendelian randomization analysis was performed to evaluate the relationship between endometriosis and PE or eclampsia using multiple methods. The analysis was stratified based on different stages and locations of endometriosis, with the number of single nucleotide polymorphisms (SNPs) ranging between 10 and 33. Below are the key findings from the MR results, categorized by method and exposure type (Figure 1).

For overall endometriosis, the Inverse Variance Weighted (IVW) method demonstrated a borderline non-significant association with PE or eclampsia ($p = 0.056$, OR = 1.0002, 95% CI = 1.0000–1.0005). In contrast, the MR Egger method showed a statistically meaningful association ($p = 0.025$, OR = 1.0009, 95% CI = 1.0002–1.0016), suggesting a possible link between endometriosis and the outcome. However, the Weighted Median and Weighted Mode methods did not find any significant associations ($p > 0.1$ for both).

In the stratified analysis of Endometriosis ASRM stages I–II, no significant association was observed using any of the methods, with the IVW method yielding a p-value of 0.060 (OR = 1.0002, 95% CI = 1.0000–1.0005), while the MR Egger, Weighted Median, and Weighted Mode methods also showed no significant findings ($p > 0.2$).

For Endometriosis ASRM stages III–IV, the IVW method detected a meaningful association ($p = 0.008$, OR = 1.0003, 95% CI = 1.0001–1.0005), suggesting a potential link between more advanced endometriosis and PE or eclampsia. Other methods, such as the MR Egger and Weighted Median, showed no statistically significant results, although the Weighted Median method approached significance ($p = 0.051$, OR = 1.0003, 95% CI = 1.0000–1.0005).

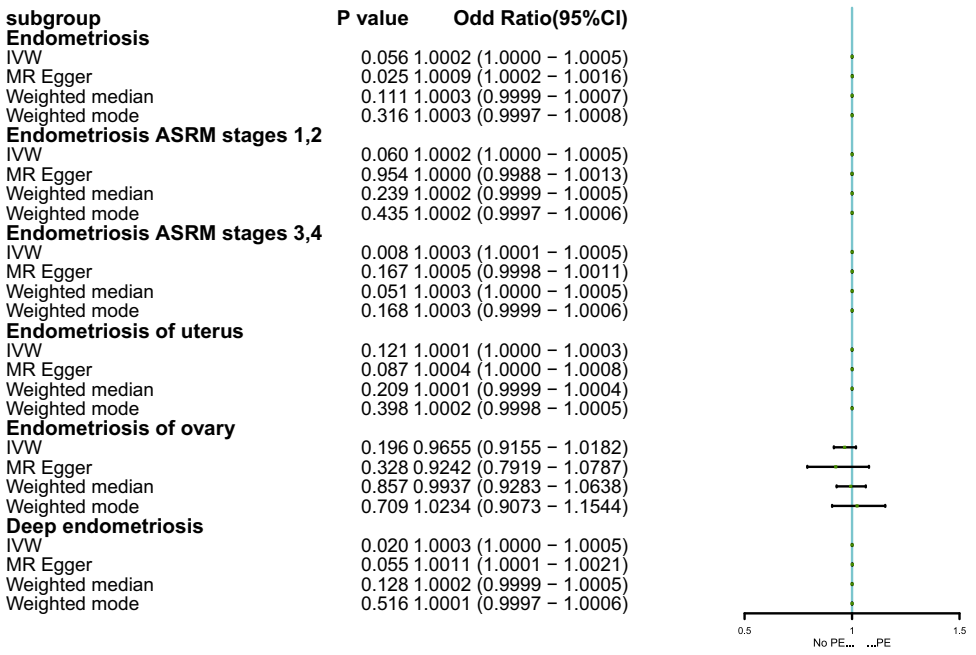

Figure 1 Association between endometriosis and preeclampsia or eclampsia.
Note: Statistical significance: $p < 0.05$.
Abbreviations: IVW, inverse-variance weighted; MR, Mendelian randomization; ASRM, American society of reproductive medicine.

In the subgroup analysis for endometriosis of the uterus, no method indicated a significant association with PE or eclampsia, as the p-values were all greater than 0.05 (eg, IVW p = 0.121, OR = 1.0001, 95% CI = 1.0000–1.0003). Similarly, analyses of endometriosis of the ovary did not yield significant findings, with the IVW method producing a p-value of 0.196 (OR = 0.9655, 95% CI = 0.9155–1.0182), and the other methods showing no strong evidence of a relationship ($p > 0.3$).

Lastly, for deep endometriosis, the IVW method suggested a meaningful association with PE or eclampsia (p = 0.020, OR = 1.0003, 95% CI = 1.0000–1.0005). The MR Egger method also approached significance (p = 0.055, OR = 1.0011, 95% CI = 1.0001–1.0021), while the Weighted Median and Weighted Mode methods showed no significant findings ($p > 0.1$).

Overall, the results suggest a potential relationship between advanced stages of endometriosis (ASRM stages III–IV) and deep endometriosis with the risk of PE or eclampsia. However, results from different MR methods were not consistent, emphasizing the need for further studies to clarify the nature of these associations.

In the retrospective observational study, 753 patients were included in the final analysis. The baseline demographic and clinical characteristics of the cohort reveal several statistically significant differences between the non-hypertension, GHD, and PE groups, as shown in Table 1. The median age was higher in the PE group (34 years) compared to the non-hypertension group (31 years), with a statistically significant difference (p = 0.002). No significant difference in BMI was

Table 1 Baseline Profiles of the Cohort

Variables	Total (n = 753)	Non-Hypertension (n = 687)	GHD (n = 11)	PE (n = 55)	p	Statistic
Age, Median (Q1,Q3)	31 (29, 34)	31 (29, 34)	31 (29.5, 34)	34 (31, 36.5)	0.002	12.555
BMI, Median (Q1,Q3)	20.94 (19.31, 22.84)	20.83 (19.32, 22.75)	21.94 (20.98, 25.9)	21.34 (18.96, 23.38)	0.255	2.731
Age of menarche, Median (Q1,Q3)	14 (13, 15)	14 (13, 15)	12 (12, 13.5)	14 (13, 14)	0.025	7.385

(*Continued*)

Table 1 (Continued).

Variables	Total (n = 753)	Non-Hypertension (n = 687)	GHD (n = 11)	PE (n = 55)	p	Statistic
Gravidity, n (%)					< 0.001	Fisher
0	373 (50)	331 (48)	8 (73)	34 (62)		
1	352 (47)	337 (49)	2 (18)	13 (24)		
2	19 (3)	14 (2)	1 (9)	4 (7)		
3	6 (1)	3 (0)	0 (0)	3 (5)		
4	3 (0)	2 (0)	0 (0)	1 (2)		
Parity, n (%)					0.017	Fisher
0	486 (65)	440 (64)	10 (91)	36 (65)		
1	263 (35)	245 (36)	1 (9)	17 (31)		
2	4 (1)	2 (0)	0 (0)	2 (4)		
History of cesarean section, n (%)					0.006	Fisher
0	707 (94)	651 (95)	10 (91)	46 (84)		
1	46 (6)	36 (5)	1 (9)	9 (16)		
History of chocolate cysts surgery, n (%)					0.848	Fisher
0	688 (91)	626 (91)	11 (100)	51 (93)		
1	65 (9)	61 (9)	0 (0)	4 (7)		
History of uterine cavity surgery, n (%)					0.145	Fisher
0	332 (44)	297 (43)	4 (36)	31 (56)		
1	421 (56)	390 (57)	7 (64)	24 (44)		
Infertility for 5 years, n (%)					0.649	Fisher
0	496 (66)	452 (66)	6 (55)	38 (69)		
1	257 (34)	235 (34)	5 (45)	17 (31)		

Note: Statistical significance: $p < 0.05$.
Abbreviations: BMI, body mass index; GHD, gestational hypertension disease; PE, preeclampsia.

observed between the groups ($p = 0.255$). The age of menarche was earlier in the GHD group, with a median of 12 years, compared to 14 years in the non-hypertension group ($p = 0.025$).

There was a statistically significant difference in gravidity between the groups ($p < 0.001$). The GHD group had a higher percentage of women with no prior pregnancies (73%) compared to 48% in the non-hypertension group. Parity also showed significant variation, with a higher proportion of nulliparous women in the GHD group (91%) compared to the non-hypertension group (64%) ($p = 0.017$).

A significant difference was found regarding the history of cesarean section, with 16% of the PE group having a previous cesarean section, compared to 5% in the non-hypertension group ($p = 0.006$). Other variables, such as operative treatment before pregnancy, history of chocolate cysts surgery, history of uterine cavity surgery, and infertility for 5 years, showed no statistically significant differences between the groups ($p > 0.05$ for all) (Table 1).

In comparing the differences between the three groups of patients with endometriosis before surgery, several significant findings emerged, as shown in Table 2. Dysmenorrhea showed a statistically significant difference across the groups ($p < 0.001$), with 73% of the GHD group and 69% of the PE group reporting dysmenorrhea compared to only

Table 2 Clinical Data and Symptoms Before EMs Surgery

Variables	Total (n = 753)	Non-Hypertension (n = 687)	GHD (n = 11)	PE (n = 55)	p	Statistic
Dyspareunia, n (%)					0.189	Fisher
0	692 (92)	630 (92)	9 (82)	53 (96)		
1	61 (8)	57 (8)	2 (18)	2 (4)		
Dysmenorrhea, n (%)					< 0.001	Fisher
0	442 (59)	422 (61)	3 (27)	17 (31)		
1	311 (41)	265 (39)	8 (73)	38 (69)		
Chronic pelvic pain, n (%)					1	Fisher
0	749 (99)	683 (99)	11 (100)	55 (100)		
1	4 (1)	4 (1)	0 (0)	0 (0)		
CA125, Median (Q1,Q3)	44.3 (27.6, 80.2)	43.7 (26.15, 80.2)	91.4 (69.6, 123.35)	44.8 (33.8, 67)	0.023	7.508
CA199, Median (Q1,Q3)	32.7 (15.89, 71.8)	32.28 (15.5, 71.8)	62.64 (45.2, 84.11)	36.06 (17.08, 70.58)	0.095	4.698
AMH, Median (Q1,Q3)	2.34 (1.34, 5.98)	2.34 (1.34, 5.98)	1.86 (1.78, 3.58)	2.82 (1.78, 5.24)	0.321	2.271

Note: Statistical significance: $p < 0.05$.

Abbreviations: AMH, anti-müllerian hormone; CA125, cancer antigen 125; CA199, cancer antigen 199; EMs, endometriosis; GHD, gestational hypertension disease; PE, preeclampsia.

39% of the non-hypertension group. No statistically significant differences were observed regarding dyspareunia ($p = 0.189$) or chronic pelvic pain ($p = 1$), with the majority of patients across all groups not reporting these symptoms.

Biochemical markers such as carbohydrate antigen 125 (CA125) and carbohydrate antigen 199 (CA199) were compared across the groups. CA125 levels were significantly higher in the GHD group (91.4) compared to the non-hypertension group (43.7) and PE group (44.8) ($p = 0.023$). CA199 levels showed a trend towards significance ($p = 0.095$), with higher median values in the GHD group (62.64) compared to the non-hypertension group (32.28). No significant differences were observed in Antimüllerian hormone (AMH) levels between the groups ($p = 0.321$) (Table 2).

The intraoperative clinical data and r-AFS scores between the three groups show several significant differences, as presented in Table 3. The r-AFS score was significantly higher in the PE group, with a median of 54, compared to 32 in the non-hypertension group ($p < 0.001$). There was no statistically significant difference in the location of chocolate cysts (unilateral or bilateral) between the groups ($p = 0.617$).

Regarding ovarian combined with peritoneal endometriosis, although there was a higher percentage in the GHD group (82%), the difference across the three groups did not reach statistical significance ($p = 0.094$). Similarly, ovarian combined with DIE did not differ significantly between the groups ($p = 0.277$).

However, there were significant differences in the diagnosis of adenomyosis, with 51% of the PE group being diagnosed, compared to only 6% in the non-hypertension group ($p < 0.001$). Uterine leiomyoma also showed a significant difference ($p = 0.002$), with 91% of the GHD group having no leiomyoma compared to 41% in the non-hypertension group. Endometrial polyps were more common in the PE group, with 18% diagnosed, compared to 7% in the non-hypertension group ($p = 0.013$) (Table 3).

The comparison of follow-up data and first full-term pregnancy data between patients with endometriosis, as shown in Table 4, reveals several notable differences. Gonadotropin-releasing hormone agonist (GnRH-a) treatment was more common in the hypertensive groups, with 91% of the GHD group and 84% of the PE group receiving treatment, compared to 72% of the non-hypertension group, although this difference did not reach statistical significance ($p = 0.067$).

A statistically significant difference was found regarding the use of assisted reproductive technology (ART) ($p < 0.001$). In the PE group, 82% of patients had used ART, compared to 24% in the non-hypertension group. Similarly, 73%

Table 3 Intraoperative Clinical Data and r-AFS Score

Variables	Total (n = 753)	Non-Hypertension (n = 687)	GHD (n = 11)	PE (n = 55)	p	Statistic
r-AFS, Median (Q1,Q3)	32 (25, 55)	32 (24, 50)	49 (28, 98)	54 (37.5, 87)	< 0.001	31.063
Chocolate cyst location, n (%)					0.617	Fisher
Unilateral	412 (55)	374 (54)	5 (45)	33 (60)		
Bilateral	341 (45)	313 (46)	6 (55)	22 (40)		
Ovarian combined with peritoneal endometriosis, n (%)					0.094	4.734
0	382 (51)	352 (51)	2 (18)	28 (51)		
1	371 (49)	335 (49)	9 (82)	27 (49)		
Ovarian combined with deep infiltrating endometriosis, n (%)					0.277	Fisher
0	680 (90)	619 (90)	9 (82)	52 (95)		
1	73 (10)	68 (10)	2 (18)	3 (5)		
Diagnosis of adenomyosis, n (%)					< 0.001	Fisher
0	681 (90)	646 (94)	8 (73)	27 (49)		
1	72 (10)	41 (6)	3 (27)	28 (51)		
Uterine leiomyoma, n (%)					0.002	Fisher
0	318 (42)	280 (41)	10 (91)	28 (51)		
1	435 (58)	407 (59)	1 (9)	27 (49)		
Endometrial polyps, n (%)					0.013	Fisher
0	692 (92)	638 (93)	9 (82)	45 (82)		
1	61 (8)	49 (7)	2 (18)	10 (18)		

Note: Statistical significance: $p < 0.05$.
Abbreviations: GHD, gestational hypertension disease; PE, preeclampsia; r-AFS: revised American Fertility Society.

of the GHD group reported using ART. There was no significant difference in the occurrence of twin pregnancies between the groups ($p = 0.125$).

The incidence of gestational diabetes mellitus was not significantly different between the groups ($p = 0.113$), with 13% in the PE group and 25% in the non-hypertension group. However, the rate of infants born small for gestational age (SGA) was significantly higher in the PE group (40%) compared to 10% in the non-hypertension group ($p < 0.001$). Lastly, the gestational age at delivery did not significantly differ between the groups ($p = 0.138$) (Table 4).

In the multivariate logistic regression analysis, the association between the r-AFS score and the risk of PE was evaluated, adjusting for various potential confounding factors across different models (Table 5).

Initially, when only the r-AFS score was included in the model, the score was meaningfully associated with an increased risk of PE (OR: 1.02, 95% CI: 1.01–1.03, $p < 0.001$), suggesting that higher endometriosis severity could increase the likelihood of PE. However, after adjusting for additional factors, this association was attenuated.

When adjustments were made for age and BMI, the r-AFS score remained a significant predictor of PE (OR: 1.02, 95% CI: 1.02–1.03, $p < 0.001$), indicating that endometriosis severity still played a role. Additionally, age was meaningfully associated with a higher risk of PE (OR: 1.16, 95% CI: 1.08–1.24, $p < 0.001$), while BMI showed no significant relationship ($p = 0.972$).

Table 4 Follow-Up Data and First Full-Term Pregnancy Data

Variables	Total (n = 753)	Non-Hypertension (n = 687)	GHD (n = 11)	PE (n = 55)	p	Statistic
GnRH-a treatment, n (%)					0.067	Fisher
0	204 (27)	194 (28)	1 (9)	9 (16)		
1	549 (73)	493 (72)	10 (91)	46 (84)		
Assisted reproductive technology, n (%)					< 0.001	Fisher
0	534 (71)	521 (76)	3 (27)	10 (18)		
1	219 (29)	166 (24)	8 (73)	45 (82)		
Twin pregnancy, n (%)					0.125	Fisher
0	675 (90)	620 (90)	10 (91)	45 (82)		
1	78 (10)	67 (10)	1 (9)	10 (18)		
Gestational diabetes mellitus, n (%)					0.113	Fisher
0	572 (76)	516 (75)	8 (73)	48 (87)		
1	181 (24)	171 (25)	3 (27)	7 (13)		
Small for gestational age, n (%)					< 0.001	Fisher
0	659 (88)	617 (90)	9 (82)	33 (60)		
1	94 (12)	70 (10)	2 (18)	22 (40)		
Gestation age (weeks) at delivery, Median (Q1,Q3)	39 (37.86, 39.86)	39 (38, 39.86)	38 (37.36, 39.86)	38.57 (37.14, 39.93)	0.138	3.965

Note: Statistical significance: $p < 0.05$.
Abbreviations: GHD, gestational hypertension disease; GnRH-a, gonadotropin-releasing hormone agonist; PE, preeclampsia.

Table 5 The Association Between the r-AFS Score and the Risk of PE

Variables	Unadjusted Model		Minimally-Adjusted Model		Moderately-Adjusted Model		Fully-Adjusted Model	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
r-AFS score	1.02	1.01, 1.03	1.02	1.02, 1.03	1.01	1.00, 1.02	1.01	0.99, 1.02
Age			1.16	1.08, 1.24	1.19	1.10, 1.29	1.20	1.10, 1.30
BMI			1.00	0.90, 1.11	0.99	0.88, 1.11	0.99	0.88, 1.11
Infertility for 5 years					0.95	0.47, 1.86	0.98	0.48, 1.92
Dysmenorrhoea					2.67	1.29, 5.65	2.72	1.31, 5.76
History of uterine cavity surgery					0.56	0.30, 1.06	0.55	0.29, 1.04
Diagnosis of adenomyosis					10.17	5.11, 0.46	9.96	5.00,0.06
GnRH-a treatment after surgery							1.63	0.72, 4.02

Note: Minimally-adjusted model: Age, BMI. Moderately-adjusted model: Age, BMI, Infertility for 5 years, Dysmenorrhoea, History of uterine cavity surgery, Diagnosis of adenomyosis. Fully-adjusted model: Age, BMI, Infertility for 5 years, Dysmenorrhoea, History of uterine cavity surgery, Diagnosis of adenomyosis, GnRH treatment after surgery.
Abbreviations: BMI, body mass index; CI, confidence interval; GnRH-a, gonadotropin-releasing hormone agonist; PE, preeclampsia; OR, odd ratio; r-AFS: revised American Fertility Society.

In the model that included factors such as infertility for 5 years, dysmenorrhea, history of uterine cavity surgery, and diagnosis of adenomyosis, the r-AFS score was no longer statistically meaningful ($p = 0.207$). In this model, age remained a significant factor (OR: 1.19, 95% CI: 1.10–1.29, $p < 0.001$), as did dysmenorrhea (OR: 2.67, 95% CI:

1.29–5.65, p = 0.009). Importantly, adenomyosis was strongly associated with PE, with a high odds ratio (OR: 10.17, 95% CI: 5.11–20.46, p < 0.001), highlighting it as a key risk factor.

Further adjustments in the final model, which accounted for GnRH-a treatment after surgery, showed similar trends. The r-AFS score was again not a significant predictor (p = 0.333). Age (OR: 1.20, 95% CI: 1.10–1.30, p < 0.001), dysmenorrhea (OR: 2.72, 95% CI: 1.31–5.76, p = 0.008), and adenomyosis (OR: 9.96, 95% CI: 5.00–20.06, p < 0.001) remained significant predictors. GnRH-a treatment after surgery did not show any significant association with PE (p = 0.264).

Discussion

In this study, we investigated the relationship between endometriosis severity and the risk of PE or eclampsia using both MR and a retrospective cohort analysis. The MR analysis suggested a potential link between advanced endometriosis (ASRM stages III–IV) and DIE with an increased risk of PE, as indicated by meaningful associations in the IVW method. However, no significant associations were found for early-stage endometriosis (ASRM stages I–II) or ovarian and uterine endometriosis. In the cohort study of 753 women with endometriosis, we observed a higher prevalence of PE among those with more severe disease, particularly in those with higher r-AFS scores (OR=1.02, p < 0.001). The r-AFS score is a continuous variable, and the OR indicates that for each additional point in the score, the risk of PE increases by several times. This OR is only 1.02, which may be due to the large range of r-AFS scores, so the increase in this OR effect value is not significant. We can confirm its statistical meaningfulness through p < 0.05. Significant differences in clinical features, such as older maternal age and higher rates of adenomyosis and assisted reproductive technology (ART) use, were noted in the PE group. These findings underscore the clinical significance of endometriosis severity in predicting PHD, particularly PE.

Our findings align with several previous studies that have highlighted the relationship between severe endometriosis and adverse pregnancy outcomes, including hypertensive disorders such as PE. For instance, a large meta-analysis conducted by Farland et al[24] found that women with laparoscopically confirmed endometriosis had a significantly increased risk of hypertensive disorders of pregnancy, including PE. This supports our observation that more advanced stages of endometriosis, particularly ASRM stages III–IV, are associated with a higher risk of developing PE. Similarly, a study by Vercellini et al[25] have identified that DIE tends to cause more severe disruptions to immune function and vascular systems, which could explain the higher risk of placental dysfunction and hypertensive outcomes in these patients. This is consistent with our findings of a higher risk of PE in women with DIE.

Further supporting our findings, Kobayashi et al[26] explored potential pathophysiological mechanisms linking endometriosis to obstetric complications, including PE. They highlighted the shared inflammatory pathways, immune dysregulation, and impaired angiogenesis that are characteristic of endometriosis and may contribute to the development of PE. Endometriosis is known to be a chronic inflammatory condition, with increased levels of inflammatory cytokines, such as interleukins (IL-6, IL-8), tumor necrosis factor-alpha (TNF-α), and prostaglandins, that can create a systemic inflammatory environment.[26] Nirgianakis K et al[27] showed that pregnant women with endometriosis, despite having undergone surgical resection of the lesion before pregnancy, are still at higher risk of developing gestational hypertension during pregnancy than normal women. This study reinforces that surgical excision alone is not a cure for the intrauterine and pelvic inflammatory environment. This inflammatory milieu may extend to the placenta, where it can disrupt trophoblast invasion and impair remodeling of the spiral arteries, both of which are critical for establishing proper uteroplacental circulation. Failure to adequately remodel the spiral arteries has been strongly implicated in the pathogenesis of PE, leading to poor placentation and placental ischemia.[24] This impaired placental development triggers a cascade of antiangiogenic factors, such as soluble fms-like tyrosine kinase-1 (sFlt-1), which further promotes endothelial dysfunction—a hallmark of PE.

Moreover, women with endometriosis often exhibit altered expression of angiogenic and anti-angiogenic factors, such as vascular endothelial growth factor (VEGF), which is essential for angiogenesis and the development of a healthy placenta. Dysregulation of VEGF and other angiogenic pathways in women with endometriosis could contribute to abnormal placentation and increase the risk of hypertensive disorders during pregnancy.[26] The imbalance between pro-inflammatory and anti-inflammatory signals in endometriosis may also impair the immune tolerance required for successful placental implantation, thereby increasing the likelihood of PE.[28] Specifically, natural killer (NK) cells,

which play a pivotal role in trophoblast invasion and immune tolerance at the maternal-fetal interface, are often functionally altered in women with endometriosis.[29] Dysfunctional NK cells may fail to properly mediate trophoblast invasion, leading to shallow implantation and an increased risk of PE.[28] In addition, due to the thicker junctional zone of the myometrium in women with endometriosis can lead to inappropriate trophoblast invasion. For the placenta to form normally, the spiral arteries in the myometrial junction zone must be converted, and various traits of this zone in individuals with endometriosis can cause abnormal placental function, thereby increasing the risk of HDP.[5]

The higher incidence of PE in women with severe forms of endometriosis, such as ASRM stages III–IV and DIE, may be explained by the degree of immune and vascular disruptions caused by more extensive disease. Severe endometriosis is associated with widespread pelvic adhesions, fibrosis, and increased density of ectopic lesions, all of which contribute to a heightened inflammatory response.[25] In advanced stages of endometriosis, the greater extent of tissue involvement likely exacerbates systemic inflammation, further impairing placentation and increasing the risk of hypertensive complications. Additionally, women with DIE often experience deeper infiltration of endometrial lesions into vital pelvic structures, leading to more profound vascular and immune alterations that could contribute to placental insufficiency and higher rates of PE.

The link between severe endometriosis and increased PE risk may also involve hormonal dysregulation. Inflammation and oxidative stress associated with severe endometriosis can disrupt endocrine signaling pathways, particularly those involving estrogen, progesterone, and cortisol, which are critical for maintaining a healthy pregnancy. Abnormal hormone levels in women with endometriosis may impair uterine receptivity and placental development, further increasing the risk of PE.[30] Studies have also shown that women with severe endometriosis have higher rates of comorbidities such as adenomyosis, which is independently associated with PE, further compounding the risk.[25]

Several key differences between our findings and previous research are worth noting. First, studies such as Zullo et al[31] and Sorrentino et al[32] did not find a significant association between endometriosis and PE, suggesting that endometriosis may not play a substantial role in hypertensive pregnancy outcomes. However, their studies did not stratify endometriosis by severity, which could explain the discrepancy with our results. In our non-stratified MR analysis, we also found no significant association between endometriosis and PE, which aligns with these earlier studies. It was only when we stratified by the severity of endometriosis (particularly ASRM stages III–IV and DIE) that we identified a clear association with PE.

Additionally, a notable difference exists regarding adenomyosis. Our MR results showed that endometriosis in the uterus (adenomyosis) is not a risk factor for PE, contrasting with observational cohort studies such as Vercellini et al,[25] which found that intraoperative detection of adenomyosis was an independent risk factor for PE. This inconsistency may stem from the lack of histopathological standards in diagnosing adenomyosis. Many observational studies rely on clinical diagnosis alone, potentially leading to inconsistent statistical approaches and conflicting outcomes.

One of the strengths of our study is the combination of MR and observational cohort analysis, offering a comprehensive view of the potential relationship between endometriosis and PE. Using genetic variants as instrumental variables, we examined the effect of endometriosis on PE while controlling for confounders. Stratifying the MR analysis by endometriosis stages and locations revealed meaningful associations between advanced endometriosis (ASRM stages III–IV) and DIE with PE, whereas early-stage endometriosis and ovarian or uterine involvement showed no significant links. This stratification approach allowed us to identify the highest-risk subtypes, which is often missed in previous studies.[24] The observational cohort of 753 women with surgically confirmed endometriosis provided real-world evidence supporting the association between disease severity and PE risk. We controlled for key confounders, such as age and parity, and found that higher r-AFS scores were meaningfully linked to increased PE risk. The large sample size and detailed clinical data strengthened the validity of our findings. Our study utilized a stratified analysis combined with MR and cohort data, providing robust evidence to elucidate the mechanistic links between endometriosis and PE. This integrated approach effectively mitigates biases inherent in each method, enabling a more comprehensive investigation of the association across diverse methodological frameworks.

Despite the strengths of our study, several limitations need to be considered. First, the MR analysis was conducted using genetic data predominantly from European populations, as stratified data for endometriosis in Asian populations are not currently available. In contrast, our cohort study was primarily based on Han Chinese women, which may limit

the generalizability of the results across different ethnic groups. Second, the MR analysis yielded non-significant odds ratios (OR) with narrow confidence intervals, reflecting limited statistical power. This may be due to the relatively small number of PE/eclampsia cases in the dataset and the limited number of single nucleotide polymorphisms (SNPs) used in the analysis, which could constrain the ability to detect meaningful associations between endometriosis and HDP.

Future studies should focus on stratifying different degrees of endometriosis to enhance the understanding of its relationship with PE. A more objective and standardized method for classifying endometriosis severity, such as imaging-based approaches or biomarker-guided stratification, could improve the accuracy of assessing disease impact on pregnancy outcomes. Additionally, expanding the availability of stratified genetic data for non-European populations, particularly Asians, would allow for more inclusive MR studies and help clarify whether the observed associations vary across ethnicities. Further, increasing the sample size in both genetic and observational studies will enhance statistical power and improve the robustness of the findings.

Conclusion

In conclusion, this study offers important insights into the association between endometriosis and PE, using a combination of MR and observational cohort data. A key strength of the study is that all patients in the observational cohort had surgically confirmed endometriosis with histological evidence, ensuring accurate diagnosis and classification. The stratified analysis of endometriosis stages, combined with genetic data, provides a deeper understanding of the potential risk factors linked to PE, particularly in women with more severe or DIE. This comprehensive approach helps shed light on the complex relationship between endometriosis severity and pregnancy outcomes, offering a strong foundation for future research in this area.

Data Sharing Statement

The cohort data used in this study are not publicly available due to privacy restrictions but can be obtained from the corresponding author, Jianying Yan (E-mail: yanjyfjmu@163.com), upon reasonable request. The genetic data for the MR analysis were sourced from publicly available GWAS datasets, with details available upon request.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki. Ethical approval for the cohort study was obtained from the Ethics Committee of Fujian Maternity and Child Health Hospital (No: 2024KY046). Written informed consent was obtained from all participants prior to inclusion in the study. For the MR analysis, only publicly available data from genome-wide association studies were used, and no additional ethical approval was required.

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Disclosure

The authors declare that there are no conflicts of interest.

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