

Effects of Previous Laparoscopic Surgical Diagnosis of Endometriosis on Pregnancy Outcomes

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Abstracts

Background: The association between the previous history of endometriosis and obstetric outcomes is still ambiguous. This study aimed to evaluate the effects of previous history of operatively diagnosed endometriosis on pregnancy outcomes.

Methods: A total of 98 primiparous women who had been diagnosed with endometriosis by previous laparoscopic surgery were included in this retrospective cohort study. Pregnancy outcomes were compared between these women (study group) who had a live birth and 300 women without endometriosis (control group) who had a live birth. In the study group, the pregnancy outcomes of 74 women who conceived naturally (no assisted reproductive technology [ART] subgroup) were simultaneously compared with 24 women who conceived by ART (ART subgroup).

Results: Miscarriage was observed in 23 of 98 women with endometriosis (23.5%). There were 75 women who had a live birth after laparoscopic diagnosis of endometriosis in the study group eventually. On multivariate analysis, the postpartum hemorrhage rate increased significantly in the study group when compared with the control group (adjusted odds ratio: 2.265, 95% confidence interval: 1.062, 4.872; $P = 0.034$). There was an upward tendency of developing other pregnancy-related complications, such as preterm birth, placental abruption, placenta previa, cesarean section, fetal distress/anemia, and others in the study group than in the control group. However, the differences showed no statistical significance. Within the study group, the occurrence rate of postpartum hemorrhage and preterm birth was both higher in the ART subgroup than in the no ART subgroup. The differences both had statistical significance (44.4% vs. 17.5%, $P = 0.024$ and 27.8% vs. 1.8%, $P = 0.010$, respectively). At the same time, median (interquartile range) for gestational age at delivery in the ART subgroup was significantly shorter than that in the no ART subgroup (38 weeks [36–39 weeks] vs. 39 weeks [38–40 weeks]; $P = 0.005$).

Conclusions: Endometriosis may affect obstetric outcomes. Women with endometriosis have a higher risk of postpartum hemorrhage. Women with endometriosis who conceived by ART may have a higher risk of postpartum hemorrhage and preterm birth than those conceived naturally.

Key words: Assisted Reproductive Technology; Endometriosis; Pregnancy Outcomes

INTRODUCTION

Endometriosis is defined as the presence of endometrial-like tissue outside the uterus, which induces pelvic pain and infertility, impairs quality of life, and reduces work productivity.^[1,2] The prevalence of endometriosis is difficult to estimate, but it affects around 11% of women worldwide and results in infertility in up to 40% of women.^[3] A growing number of studies have revealed that endometriosis may have a negative impact on pregnancy and may increase the risk of adverse obstetric outcomes. A recent retrospective cohort study determined the effect of endometriosis on obstetric outcomes in Chinese women with endometriosis.

It concluded that women with endometriosis are at a higher risk of preterm labor, placenta previa, and cesarean section during pregnancy.^[4] Another study, however, reached the opposite conclusion, highlighting that it is well documented that endometriosis may not affect pregnancy outcome.^[5] The

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results from previous studies examining the link between endometriosis and adverse pregnancy outcomes are inconsistent.^[6]

In addition, many patients with endometriosis achieve pregnancy through assisted reproductive technology (ART), which may independently affect pregnancy outcomes. A recent meta-analysis explored whether there are any increases in pregnancy-related complications and adverse pregnancy outcomes in singleton pregnancies after ART compared with those who conceived naturally. This study indicated that the singleton pregnancies created with ART experienced a significantly increased risk compared with those conceived naturally.^[7] Thus, it is difficult to determine the specific contribution of endometriosis to poor pregnancy outcomes relative to the interventions required for successful pregnancy.^[8]

Therefore, we conducted a study to evaluate the association between the previous history of endometriosis and obstetric outcomes. We also compared the pregnancy outcomes of women with endometriosis conceived by ART with those who conceived naturally.

METHODS

The retrospective study was approved by the Institutional Review Board of the Peking University People's Hospital. Informed consent was waived due to the retrospective nature of this study.

Patients

We investigated 98 women who had been diagnosed with endometriosis in the Department of Obstetrics and Gynecology, Peking University People's Hospital, from 2011 to 2013. These women attended routine prenatal check-ups throughout the whole pregnancy and delivered in the same hospital. Endometriosis was evaluated according to the revised American Society for Reproductive Medicine (rASRM) classification. In the study group, 54 women were diagnosed with Stage I/II endometriosis, and 44 women were diagnosed with Stage III/IV endometriosis. Miscarriage was observed in 23 women in the study group including 22 cases of early abortion and one case of late abortion. According to the rASRM classification, among patients who suffered miscarriage, nine women were diagnosed with Stage I/II endometriosis, and 14 women were diagnosed with Stage III/IV endometriosis. Seventy-five women achieved a birth in the study group. Participants in the control group included 300 women who had no gynecological diseases before gestation and achieved singleton pregnancies during the same period in the same hospital, who were randomly allocated by a computer-generated randomization scheme with a 4:1 allocation for the study. This study aimed to estimate the risk for adverse pregnancy outcomes among women in the study group compared with those in the control group. In addition, the study also compared the pregnancy outcomes within the study group between those who got pregnant by ART (ART subgroup) and those who conceived

naturally (no ART subgroup). All women were nulliparous and achieved singleton pregnancies. Adverse pregnancy outcomes included hypertensive disorders of pregnancy, postpartum hemorrhage, cesarean section, preterm birth, placental abruption, and fetal distress/anemia. Neonatal outcomes included Apgar score, birth weight, and gestational age at delivery.

Inclusion and exclusion criteria

The study group inclusion criteria were (1) women who had undergone laparoscopic surgery for endometriosis, (2) women aged between 21 and 40 years, and (3) women who attended routine prenatal check-ups throughout their whole pregnancy and delivered in the same hospital. The exclusion criteria of the two groups were women with malignancies, adenomyosis, immune system diseases, endocrine diseases, cardiovascular diseases, and other complications. Women with suspected symptoms of endometriosis but absence of surgical confirmation were also excluded from the study.

Statistical analysis

Data were calculated using the SPSS 22.0 software package for Windows (SPSS Inc., USA). Categorical variables, such as frequency distribution of hypertensive disorders of pregnancy, postpartum hemorrhage, cesarean section, preterm birth, and placental abruption, were compared using the Chi-square test or Fisher exact test. Continuous variables, such as maternal age, birth weight, and gestational age at delivery, were compared using Student's *t*-test or Mann-Whitney U-test. Binary and multinomial logistic regression models were used to evaluate the difference between the ART subgroup and the no ART subgroup on adverse pregnancy outcomes. Adjusted odds ratios (*ORs*) with 95% confidence intervals (*CI*s) were obtained after adjusting for related factors. A value of $P < 0.05$ was considered to indicate statistical significance.

RESULTS

This retrospective cohort study was carried out from January 2011 to December 2013. In the study, 398 women, including 98 women in the study group and 300 women in the control group, were analyzed to investigate pregnancy outcomes. Miscarriage was observed in 23 of the 98 women in the study group. Sociodemographic characteristics of participants are shown in Table 1. Compared with those in the control group, women in the study group who had a live birth were of higher age at delivery (32.8 ± 3.4 vs. 30.1 ± 2.9 , $P < 0.001$) and were more likely to have higher pregnancy parities ($P = 0.001$). No other statistically significant differences between the two groups were found.

As shown in Table 2, pregnancy outcomes were analyzed in the study group and control group. Multiple analyses were applied by means of the logistic regression model, adjusting for age at delivery and pregnancy parity. It showed that the study group had a significantly increased risk of postpartum hemorrhage (adjusted *OR*: 2.265, 95% *CI*: 1.062–4.872),

compared with the control group. At the same time, the incidence for such complications as gestational diabetes mellitus (18.7% vs. 11.0%), placental abruption (22.7% vs. 19.3%), placenta previa (2.7% vs. 1.7%), preterm birth (8% vs. 5%), cesarean section (42.7% vs. 33.3%), fetal distress/anemia, and others (41.3% vs. 45.3%) were higher in study group although the differences had no statistical significance. Table 3 shows the sociodemographic characteristics in the ART and no ART subgroups. The ART subgroup had a statistically significantly increased risk of infertility history compared to the no ART subgroup (66.7% vs. 26.7%). No statistically significant differences were found in any other comparisons.

Pregnancy outcomes in the ART and no ART subgroups are presented in Table 4. The miscarriage rates of the two groups were 25.0% and 23.0%, respectively. No statistically

significant differences were found ($P = 0.839$). After adjusting for age at delivery and infertility, the ART group demonstrated a significantly higher likelihood of developing postpartum hemorrhage (adjusted $OR: 4.169$, 95% $CI: 1.204-14.427$) and preterm birth (adjusted $OR: 22.473$, 95% $CI: 2.135-236.592$) than the no ART subgroup. The median (interquartile range) for gestational age at delivery in the two groups was 38 weeks (36-39 weeks) for the ART subgroup and 39 weeks (38-40 weeks) for the no ART subgroup, respectively ($P = 0.005$). The time interval between operation and pregnancy in the ART subgroup was significantly longer than in the no ART subgroup (15.4 ± 11.8 vs. 9.7 ± 6.9 months, $P = 0.013$). No statistically significant differences were found in any other comparisons, such as the occurrence of gestational diabetes mellitus, hypertensive disorders of pregnancy, placenta

Table 1: Sociodemographic characteristics of study participants

Characteristics	Endometriosis (n = 75)	No endometriosis (n = 300)	Statistics	P
Age at delivery (years), mean \pm SD	32.8 \pm 3.4	30.1 \pm 2.9	6.670*	<0.001
Pregnancy parity, n (%)				
1	59 (78.7)	174 (58.0)	10.260*	0.001
≥ 2	16 (21.3)	126 (42.0)		
Age at menarche (years), median (interquartile range)	13 (12, 14)	14 (13, 14)	-0.425 [‡]	0.671
BMI (kg/m ²), median (interquartile range)	21.2 (19.6, 23.0)	21.5 (19.5, 23.4)	-0.690 [‡]	0.490

*t values; [†] χ^2 values; [‡]Z values. SD: Standard deviation; BMI: Body mass index.

Table 2: Analysis of pregnancy outcomes in women with and without endometriosis

Pregnancy outcomes	Endometriosis (n = 75)	No endometriosis (n = 300)	Adjusted OR* (95% CI)	P
Postpartum hemorrhage, n (%)	18 (24.0)	38 (12.7)	2.265 (1.062-4.872)	0.034
GDM, n (%)	14 (18.7)	33 (11.0)	1.217 (0.528-2.804)	0.645
Placental abruption, n (%)	17 (22.7)	58 (19.3)	1.386 (0.675-2.848)	0.374
Hypertensive disorders of pregnancy, n (%)	2 (2.7)	19 (6.3)	0.471 (0.095-2.342)	0.357
Placenta previa, n (%)	2 (2.7)	5 (1.7)	0.557 (0.076-4.102)	0.566
Preterm birth, n (%)	6 (8.0)	15 (5.0)	1.301 (0.339-4.245)	0.663
Cesarean, n (%)	32 (42.7)	100 (33.3)	1.532 (0.827-2.836)	0.175
Fetal distress/anemia and others, n (%)	31 (41.3)	106 (35.3)	1.631 (0.886-3.002)	0.116
Apgar score, 5 min <7	0	1	-	-
Birth weight (g), median (interquartile range)	3410 (3105, 3657)	3360 (3080, 3650)	-	0.488
Gestational age at delivery (weeks), median (interquartile range)	39 (38, 40)	39 (38, 40)	-	0.188

*Adjusting for age at delivery, pregnancy parity. OR: Odd ratio; CI: Confidence interval; GDM: Gestational diabetes mellitus.

Table 3: Sociodemographic characteristics of study group

Characteristics	No ART (n = 74)	ART (n = 24)	Statistics	P
Age at delivery (years), mean \pm SD	30.8 \pm 3.4	32.1 \pm 3.2	-1.789*	0.077
Pregnancy parity, n (%)				
1	44 (59.5)	14 (59.2)	0.010*	0.922
≥ 2	30 (40.5)	10 (40.8)		
Age at menarche (years), median (interquartile range)	13 (12, 14)	13 (12, 14)	-0.035 [‡]	0.972
Infertility, n (%)	22 (29.7)	16 (66.7)	11.680*	0.001
rASRM stages, n (%)				
I/II	43 (58.1)	11 (45.8)	1.104 [†]	0.293
III/IV	31 (41.9)	13 (54.2)		

*t values; [†] χ^2 values; [‡]Z values. ART: Assisted reproductive technology; SD: Standard deviation; rASRM: Revised American Society for Reproductive Medicine.

abruption, placenta previa, fetal distress/anemia, preterm birth, cesarean section, and birth weight. Table 5 indicated the comparison between rASRM Stages III/IV and rASRM Stages I/II in terms of spontaneous miscarriage and ART rate. Spontaneous miscarriage rate in Stage III/IV group was higher than it in Stage I/II group (31.8% vs. 16.7%, *OR*: 2.330, 95% *CI*: 0.897–6.027; *P* = 0.078). The ART rate was higher in Stage III/IV group than that in Stage I/II group (29.5% vs. 20.4%, *OR*: 1.639, 95% *CI*: 0.649, 4.139; *P* = 0.239).

DISCUSSION

Findings from our study indicated that the study group was of a higher age at delivery and had more pregnancy parities before having a live birth, than the control group. Miscarriage was observed in 23 of 98 women with endometriosis (23.5%). This was higher than the general population, which was reported at approximately 9% in a previous study.^[9] After adjusting for confounding factors, the study group had an increased risk of postpartum hemorrhage compared with the control group (*P* = 0.034). There was an upward tendency of developing other pregnancy-related complications, such as preterm birth, placental abruption, placenta previa, cesarean section, fetal distress/anemia and others in the study group than in the control group. However, the differences showed no statistical significance. No significant difference was found in neonatal outcomes, including Apgar score, birth weight, and gestational age at delivery, indicating that endometriosis had no effect on neonatal outcomes, but it did have an effect on adverse pregnancy outcomes. Endometriosis may also influence the miscarriage rate. Women with Stage III/IV endometriosis had higher risk

of spontaneous abortion and ART rate than those with Stage I/II.

The incidence of obstetric outcomes in women with endometriosis is controversial. Several authors found that women with endometriosis often had adverse pregnancy outcomes, which is consistent with our findings.^[2,5,10] In a nationwide Scottish study, endometriosis was found to predispose women to an increased risk of placenta previa, postpartum hemorrhage, and preterm birth in progressing pregnancies.^[2] An Australian retrospective cohort study reported that the pregnancy complications of women with endometriosis who conceived by ART involved more instances of primary postpartum hemorrhage (1.3, 1.1–1.6), and placenta previa (1.7, 1.2–2.4) than in those without endometriosis.^[11] A Chinese retrospective cohort study also certified the effect of endometriosis on pregnancy outcomes and obtained a similar result.^[4] The existing data linking endometriosis with pregnancy outcomes are predisposed to be adverse. However, some studies have found that endometriosis does not affect pregnancy outcomes.^[6,7] Endometriosis with hypertensive disorders of pregnancy continues to be a controversial health issue. In our study, the significance difference of gestational hypertension/preeclampsia was not found between study group and control group. Our results are distinct to those of the previous studies,^[2,5,12] but a Canadian study reported a similar finding. The study reported the absence of any association between gestational hypertension/preeclampsia and endometriosis.^[13] These results suggest that clinicians should provide increased care for women with endometriosis.

The incidence of pregnancy outcomes in patients with endometriosis, achieving pregnancy spontaneously or

Table 4: Analysis for pregnancy outcomes in women with endometriosis

Pregnancy outcomes	No ART (<i>n</i> = 74)	ART (<i>n</i> = 24)	Adjusted <i>OR</i> * (95% <i>CI</i>)	<i>P</i>
Postoperative pregnancy time (months), mean ± SD	9.7 ± 6.9	15.4 ± 11.8	–	0.013
Postpartum hemorrhage, <i>n</i> (%)	10 (17.5)	8 (44.4)	4.169 (1.204–14.427)	0.024
GDM, <i>n</i> (%)	9 (15.8)	5 (27.8)	1.440 (0.361–5.751)	0.606
Placental abruption, <i>n</i> (%)	14 (24.6)	3 (16.7)	0.730 (0.179–3.156)	0.697
Hypertensive disorders of pregnancy, <i>n</i> (%)	1 (1.8)	1 (5.6)	3.772 (0.137–103.612)	0.432
Placenta previa, <i>n</i> (%)	0	2 (11.1)	–	0.055
Fetal distress/anemia, <i>n</i> (%)	23 (40.4)	8 (44.4)	1.054 (0.336–3.307)	0.928
Preterm birth, <i>n</i> (%)	1 (1.8)	5 (27.8)	22.473 (2.135–236.592)	0.010
Cesarean section, <i>n</i> (%)	22 (38.6)	10 (55.6)	1.987 (0.608–4.496)	0.256
Birth weight (g), median (interquartile range)	3480 (3170, 3680)	3350 (2540, 3650)	–	0.217
Gestational age at delivery (weeks), median (interquartile range)	39 (38, 40)	38 (36, 39)	–	0.005

*Adjusting for age at delivery, infertility. ART: Assisted reproductive technology; *OR*: Odds ratio; *CI*: Confidence interval; SD: Standard deviation; GDM: Gestational diabetes mellitus.

Table 5: Comparison between rASRM Stages III/IV and rASRM Stages I/II in terms of spontaneous miscarriage and ART rate

Characteristics	rASRM Stage III/IV (<i>n</i> = 44)	rASRM Stage I/II (<i>n</i> = 54)	<i>OR</i> (95% <i>CI</i>)	<i>P</i>
Spontaneous miscarriage, <i>n</i> (%)	14 (31.8)	9 (16.7)	2.330 (0.897–6.027)	0.078
ART, <i>n</i> (%)	13 (29.5)	11 (20.4)	1.639 (0.649–4.139)	0.239

rASRM: Revised American Society for Reproductive Medicine; *OR*: Odds ratio; *CI*: Confidence interval; ART: Assisted reproductive technology.

through ART, is controversial. Previous studies have concentrated on the association between endometriosis and *in vitro* fertilization (IVF) outcome. These studies, however, did not take into account that women with endometriosis who conceived by ART have been linked to a spectrum of major pregnancy complications. Harb *et al.*^[14] published a meta-analysis with the association between endometriosis and IVF outcome; the outcomes were fertilization, implantation, clinical pregnancy rates, and live birth rates; patients were classified by their stage of endometriosis; their meta-analysis found that the presence of severe endometriosis (Stage III/IV) reduces implantation and clinical pregnancy rates in women undergoing IVF treatment; however, they included some studies in which diagnostic laparoscopy was used to confirm the presence of endometriosis, whereas some studies reported diagnosis based on ultrasonographic findings. Many other studies showed the impact of endometrioma on IVF/intracytoplasmic sperm injection outcomes as compared to patients without endometriosis. The presence of endometriosis does not adversely affect IVF outcomes in terms of live birth.^[15-17] Senapati *et al.*^[18] also assessed the impact of endometriosis on IVF outcomes. They concluded that endometriosis was associated with lower pregnancy rates after IVF. In another case-control study, Jacques *et al.*^[12] reported adverse pregnancy and neonatal outcomes after ART in patients with pelvic endometriosis. Compared with the control group selected among ART pregnancies due to male infertility, the incidence of first trimester bleeding, preeclampsia, premature delivery threat, and cesarean section was significantly higher ($P < 0.05$) in women with endometriosis. It is still difficult to distinguish the specific contribution of endometriosis from ART to poor pregnancy outcomes. Our study was a randomized controlled trial that evaluated the influence of ART based on endometriosis on adverse pregnancy outcomes. The analyses showed that the ART subgroup had a significantly increased risk of postpartum hemorrhage and preterm birth compared with no ART subgroup ($P = 0.024$ and $P = 0.010$, respectively). The time interval between operation and pregnancy in the ART subgroup was significantly longer than in the no ART subgroup (15.4 ± 11.8 vs. 9.7 ± 6.9 months, $P = 0.013$). In other words, women with endometriosis who conceived by ART required much more times to have a baby. Gestational age at delivery in the ART subgroup was significantly shorter than in the no ART group. The rates of other adverse pregnancy outcomes were not significantly different between the two groups, and no significant differences in neonatal outcomes were found. The measures of our study were adapted to the parameters of a recent study,^[19] which did not report the birth weight and gestational age at delivery; though the recent study included a large numbers of patients, the diagnostic adverse outcomes information is incomplete. Further study of the pregnancy outcomes for women with endometriosis who conceive by ART treatment is still needed.

The underlying mechanisms involved in the association between endometriosis and adverse obstetric outcomes

in singleton pregnancies are uncertain. Endometriosis is associated with a chronic pelvic inflammatory process, and the activation of inflammatory pathways could stimulate myometrial contractions and cervical ripening, leading to preterm labor.^[20] It also remains difficult to determine the contribution of ART to poor pregnancy outcomes. Some studies have reported that factors associated with ART procedures themselves may increase the risk of adverse outcomes. ART and the transfer of embryos decrease vascular cell proliferation and the density of blood vessels, resulting in the dysfunctional implantation of the embryo and trophoblast invasion into the receptive maternal decidua.^[21,22] Our study may provide the direction for further research of the underlying mechanisms between endometriosis and adverse obstetric outcomes.

Our study not only showed the effect of endometriosis on adverse obstetric outcomes, but also concentrated on the association between ART and obstetric outcomes in women with endometriosis. The key strengths of the study lie in women with endometriosis who were confirmed histologically and visually during a surgical procedure in our hospital, which reduced the risk of different medical technology usage. Furthermore, all participants were delivered in our obstetric department, which ensured integrity and authenticity of the dates. A cohort study showed women at first pregnancy had an increased risk of impaired obstetric outcome compared to multiparous women.^[23] Therefore, we did not include multiparous women in our study to avoid bias. Finally, our study collected data concerning disease stage based on the American Society for Reproductive Medicine classification and addressed the use of revised American Fertility Society (rAFS) stage and score as risk factors.^[24,25] In the study group, based on the means of pregnancy for women with endometriosis, clinicians could evaluate the effects of the rAFS stage on the means of pregnancy.

However, some limitations exist in our study. First, the endometriosis group contains only a small number of participants. After laparoscopic surgery for endometriosis in our hospital, many patients chose to deliver in their primary hospital. Second, an inherent bias is present in the data collection of retrospective studies.

In conclusion, endometriosis may affect obstetric outcome. Women with endometriosis have a higher risk of postpartum hemorrhage. They also have an increased trend of developing preterm birth, placental abruption, placenta previa, cesarean, fetal distress/anemia, etc., Women with endometriosis who conceived by ART may have a higher risk of postpartum hemorrhage and preterm birth than those who conceived naturally. This suggests that women with endometriosis, especially those who conceived by ART, require additional care during pregnancy and delivery.

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Conflicts of interest

There are no conflicts of interest.

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