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Original Research

Perinatal Outcomes were Associated with the Positional Relationship between Placenta and Adenomyotic Lesion in Pregnant Patients with Adenomyosis

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Abstract

Background: The adverse perinatal outcome caused by adenomyosis has been widely concerned recently, but little attention has been paid to whether the positional relationship between placenta and adenomyotic lesion influences the maternal and perinatal outcomes. **Methods**: A total of 311 women with adenomyosis who were pregnant greater than 20 weeks gestation and delivered at Women's Hospital, Zhejiang University School of Medicine between January 2010 and December 2021 were recruited. The positional relationships between placenta and adenomyotic lesions were determined. The patients were divided into two subgroups: group 1, placenta located on or above the adenomyotic lesion; and group 2, placenta located far away from the adenomyotic lesion. The clinical data of two groups were retrospectively analyzed. **Results**: We found a higher rate of diffuse adenomyosis (62.65% *vs*. 46.21%, $p = 0.01$), coexisting endometriosis (31.93% *vs*. 15.86%, $p = 0.002$), preterm delivery (34.94% *vs*.15.17%, $p < 0.001$) and placenta malposition (19.88% *vs*. 6.90%, $p = 0.002$) in group I compared to group II. Compared with group II, group I had lower birth weight ($p = 0.02$). After adjustment using multiple logistic regression analysis, maternal adverse outcome was only correlated with age ($p = 0.02$). Neonatal adverse outcomes were closely correlated with group I ($p = 0.004$), including pregnancy induced hypertension ($p = 0.01$), placenta malposition ($p = 0.02$), placental abruption ($p = 0.003$), and scarred uterus ($p = 0.02$). **Conclusions**: The positional relationships between the placenta and adenomyotic lesions were graphically presented. Placental position near or above adenomyosis lesions might correlate to the adverse perinatal outcomes of pregnant women with adenomyosis and thereby deserve more attention.

Keywords: adenomyosis; pregnancy; perinatal outcome; placenta; adenomyotic lesion

1. Introduction

Adenomyosis, an estrogen-dependent chronic inflammatory gynecological benign disease, is defined as the presence of endometrial glands and stroma within the myometrium of the uterus, resulting in dysmenorrhea and infertility [1–3]. The exact pathogenesis of adenomyosis remains unclear, although the incidence of adenomyosis tends to occur in younger women and is rising [4–6]. Although there are many mechanisms to explain infertility caused by adenomyosis, such as abnormal endometrial receptivity and oviduct peristalsis, it is still not clear whether infertility is the result or the cause of adenomyosis [6–9]. Recently, as more women delay their first pregnancy, adenomyosis, like endometriosis, is attracting more attention because of its increasing impact on fertility and pregnancy outcomes [10–17]. Consequently, it is necessary to identify the high risk factors affecting the fertility and reproductive outcomes of patients with adenomyosis prior to pregnancy in order to minimize obstetric complications.

Increasing evidence from recent studies has demonstrated that many factors, including age, uterine size, disease severity, subtype and concomitant diseases, can affect the pregnancy outcomes of women with adenomyosis [18–24]. One study of uterus-sparing surgery for patients with adenomyosis by Kishi *et al*. [18] showed that the clinical pregnancy rate of women $\leq$39 years old (41.3%) was significantly higher than that of women $\geq$40 years old (3.7%). Another study of frozen thawed embryo transfer for patients with adenomyosis by Li *et al*. [19] found that the miscarriage rate of women with large uterine volume (>98.81 cm^3) was 8.5 times that of women with small uterine volume ($\leq$98.81 cm^3). Using the new ultrasonographic adenomyosis grading and severity scoring system, it was found that the higher the score of adenomyotic lesions was associated with higher infertility and miscarriage rates [20]. It has been shown that the clinical pregnancy rate of women with focal adenomyosis is higher than that of women with diffuse adenomyosis following uterus-sparing surgery [21]. Compared with women with adenomyosis alone, women with the combination of adenomyosis and endometriosis have a higher miscarriage rate and a lower live birth rate [22–24].

Many obstetric complications in pregnant women with adenomyosis, such as preeclampsia, preterm birth, premature rupture of membrane, small for gestational age, malp-

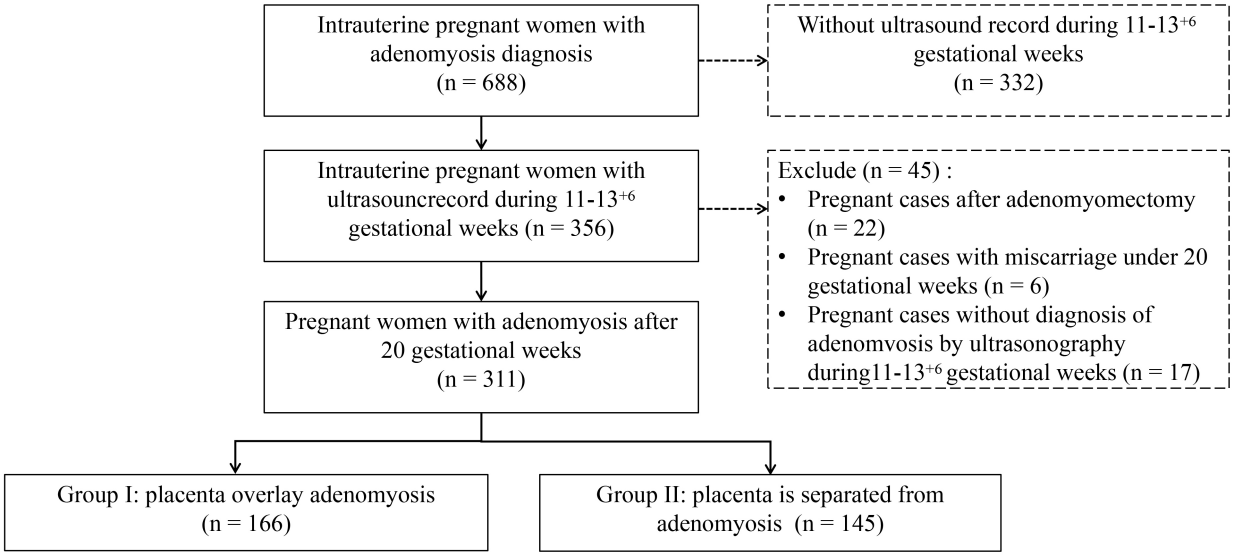

Fig. 1. Flow chart of patient inclusion.

resentation and abruption have received more attention in recent years [25–28]. More recently, a study by Ono *et al*. [29] of the positional relationship between the placenta and the adenomyosis lesion influenced the perinatal outcomes demonstrating that placental localization near or above adenomyotic lesions increased the risk of perinatal complications. Based on previous research, we performed a retrospective study [30], and found that our results were consistent with those reported by Ono *et al*. [29]. There was a significant increase in the obstetric morbidity and lower birth weight when the placenta overlaid an adenomyosis lesion. If women with severe diffuse adenomyosis do not have normal myometrium, their placenta will be implanted on the adenomyotic lesions. This may be the cause of infertility or pregnancy failure in patients with severe diffuse adenomyosis.

We investigated if the positional relationship between placenta and adenomyotic lesions could be identified in pregnant women with adenomyosis, and all patients were divided into two subgroups (Group 1: placenta on or above the adenomyotic lesion; Group 2: placenta far away from the adenomyotic lesion) according to the relationship between placental implantation site and the adenomyotic lesion. A comparative analysis was performed so as to clarify the influence of the relationship between placental implantation site and adenomyosis lesion on perinatal complications.

2. Materials and Methods

2.1 Patients

Between January 2010 and December 2021, a total of 688 pregnant women with adenomyosis who delivered at Women's Hospital, School of Medicine, Zhejiang University were recruited for this study. The clinical data of all pregnant women with adenomyosis, including age, gravidity, parity, history of surgery, hormone therapy, adenomyosis subtype, gestational age, natural pregnancy, assisted reproductive technology (ART) pregnancy, comorbidity, pregnancy induced hypertension (PIH), gestational diabetes mellitus (GDM), fetal growth restriction (FGR), placental abnormalities, premature rupture of fetal membranes (PROM), preterm birth, mode of delivery, size of the placenta, neonatal birth weight, and postpartum hemorrhage were retrospectively obtained and recorded from the original electronic medical record (EMR) of hospitalized pregnant women with adenomyosis. This study was approved by the Ethics Committee of Women's Hospital, School of Medicine, Zhejiang University (No. IRB-20210310-R). All patients were exempt from informed consent because this study was retrospective.

Of the 688 pregnant women with adenomyosis, 332 were excluded because there were no nuchal translucency (NT) ultrasound records during 11–13^{+6} weeks of gestation. Next, 45 pregnant women with adenomyosis, including 22 cases after adenomyomectomy, 6 cases of miscarriage before 20 weeks of pregnancy and 17 cases of adenomyosis who were not diagnosed by ultrasound during 11–13^{+6} weeks of gestation, were also excluded. The remaining 311 pregnant women with adenomyosis had a gestational age of >20 weeks. Detailed NT ultrasound records clearly showed the relationship between the placental implantation site and adenomyotic lesion at 11–13^{+6} weeks of gestation, and they were divided into two groups: Group I (n = 166) indicated that the placenta was located on the adenomyotic lesion; Group II (n = 145) exhibited that the placenta was far away from the adenomyotic lesion (Figs. 1,2).

2.2 Ultrasonographic Diagnosis of Adenomyosis

In order to avoid deviation, two experienced ultrasound experts who were not involved in the research re-

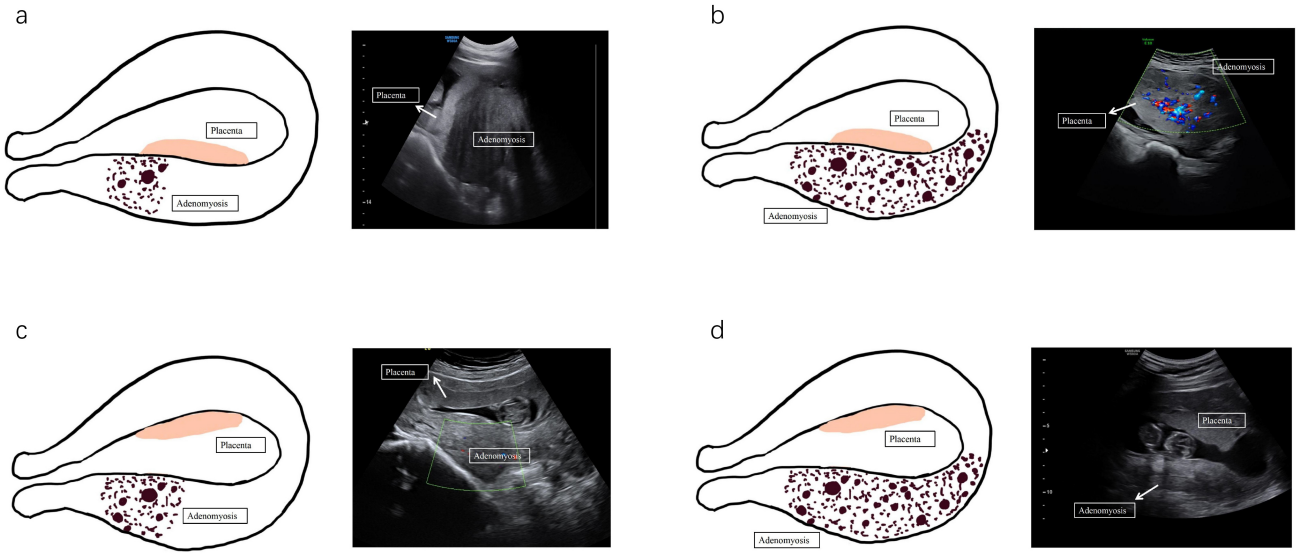

Fig. 2. The diagram of the positional relationships between placenta and adenomyotic lesion. Group I: the placenta was located on the adenomyotic lesion (as shown in (a,b)). Group II: the placenta was far away from the adenomyotic lesion (c,d).

Table 1. The characteristics of included patients in two groups.

	Overall (n = 311)	Group I (n = 166)	Group II (n = 145)	*p*
Age (mean (SD))	34.39 (4.53)	34.09 (4.36)	34.72 (4.70)	0.22
Age group (%)				
<35 years	156 (50.16)	86 (51.81)	70 (48.28)	0.61
≥35 years	155 (49.84)	80 (48.19)	75 (51.72)	
Parity (%)				
0	123 (39.55)	62 (37.35)	61 (42.07)	0.46
≥1	188 (60.45)	104 (62.65)	84 (57.93)	
ART (%)	69 (22.19)	40 (24.10)	29 (20.0)	0.47
Adenomyosis type (%)				
Focal	140 (45.02)	62 (37.35)	78 (53.79)	0.005
Diffuse	171 (54.98)	104 (62.65)	67 (46.21)	
Pre-pregnant hysterauxesis (%)*	41 (18.30)	21 (18.58)	20 (18.02)	1.00
Scarred uterus (%)	133 (42.77)	63 (37.95)	70 (48.28)	0.09
History of endometriosis (%)	76 (24.44)	53 (31.93)	23 (15.86)	0.002

SD, standard deviation; ART, assisted reproductive technology.

*Pre-pregnant uterine enlargement was defined as the volume of uterus larger than 3 months of gestation; there were 87 women without the data of pre-pregnancy uterus volume.

examined the ultrasound images to confirm the diagnosis of adenomyosis and the positional relationship between placenta and adenomyotic lesion. The ultrasonic diagnostic criteria for adenomyosis were formulated according to the 2022 consensus on the revised definition of morphological ultrasound assessment (MUSA) features of adenomyosis [31].

2.3 Statistical Analysis

Summary statistics were used to characterize the study population and differences between groups were assessed using Chi-square or Fisher's exact test for categorical variables, Student's *T* test for normally distributed continuous variables and Mann–Whitney U tests for non-normally distributed data. Multiple logistic regression analyses were used to determine the association between factors and preterm birth if the placenta was located above adenomyosis. Covariates in the multivariate models were selected based on a significant association at alpha <0.10 level in univariate analysis. Odds ratios (ORs) and 95% confidence intervals (CIs) are presented. Spearman correlation analysis was used to assess the association between placental surface area and birth weight. p-value < 0.05 was considered statistically significant. The clinical data were analyzed using R version 4.2.1 (the R Foundation, Vienna, Austria).

Table 2. Clinical outcomes of included patients in two groups.

	Overall (n = 311)	Group I (n = 166)	Group II (n = 145)	*p*
Cervical incompetence (%)	12 (3.86)	7 (4.22)	5 (3.45)	0.96
PIH (%)	45 (14.47)	20 (12.05)	25 (17.24)	0.26
GDM (%)	60 (19.29)	29 (17.45)	31 (21.38)	0.47
Oligohydramnios (%)	15 (4.82)	8 (4.82)	7 (4.83)	1.00
FGR	23 (7.40)	15 (9.04)	8 (5.52)	0.33
PROM (%)	47 (15.11)	23 (13.86)	24 (16.55)	0.62
Uterine rupture or threatened uterine rupture (%)	2 (0.64)	2 (1.20)	0 (0.00)	0.54
Preterm delivery (%)	80 (25.72)	58 (34.94)	22 (15.17)	<0.001
Fetal presentation (%)				
Cephalic	301 (96.78)	159 (95.78)	142 (97.93)	0.45
Non-cephalic	10 (3.22)	7 (4.22)	3 (2.07)	
5 min Apgar <7 (%)	11 (3.54)	9 (5.42)	2 (1.38)	0.11
Delivery mode (%)				
Vaginal delivery	61 (19.61)	36 (21.69)	25 (17.24)	0.40
Cesarean delivery	250 (80.39)	130 (78.31)	120 (82.76)	
Birth weight (median (IQR))	3090 (2580, 3400)	3050 (2350, 3335)	3100 (2800, 3415)	0.02
Placenta malposition (%)*	43 (13.83)	33 (19.88)	10 (6.90)	0.002
Placental abruption (%)	11 (3.54)	6 (3.61)	5 (3.45)	1.00
Placental surface area (median (IQR))	324 (288, 360)	323 (256, 360)	342 (306, 360)	0.004
Blood loss during delivery (median (IQR))	300 (200, 400)	300 (200, 400)	300 (200, 400)	0.40
Postpartum hemorrhage	23 (7.40)	15 (9.04)	8 (5.52)	0.33
Composite neonatal adverse outcomes (%)	99 (31.83)	70 (42.17)	29 (20.00)	<0.001
Composite maternal adverse outcomes (%)	124 (39.87)	65 (39.16)	59 (40.69)	0.87

PIH, pregnancy induced hypertension syndrome; GDM, gestational diabetes mellitus; FGR, fetal growth restriction; PROM, premature rupture of fetal membranes; IQR, interquartile range.

*Placental malposition includes placenta previa or low-lying placenta.

Neonatal adverse outcomes including: preterm delivery, FGR and 5 min Apgar <7.

Maternal adverse outcomes including: PIH, GDM, uterine rupture or threatened uterine rupture, placental abruption and postpartum hemorrhage.

3. Results

3.1 Patients' Characteristics

In this study, the patients were screened as shown in Fig. 1. The final study included 311 pregnant women with adenomyosis. The mean age was 34.39 $\pm$ 4.53 years old. Among them, 140 (45.02%) cases were focal adenomyosis and 171 (54.98%) cases were diffuse adenomyosis respectively. In these two groups, there were 123 (39.55%) primiparas, 69 (22.19%) cases conceived through assisted reproductive technology (ART) and 133 (42.77%) cases with a scarred uterus. Seventy six (24.44%) cases had coexisting endometriosis. There were 87 women without the data of pre-pregnancy uterine size. Among women with data of pre-pregnant uterine size, 41 (18.30%) cases had pre-pregnant uterine size larger than three months of gestation (Table 1). Uterine volume was assumed as an ellipsoid shape and calculated using the following formula: $\pi/6 \times$ length $\times$ width $\times$ depth (three months of gestation uterine $\approx$ 300 cm^3). The length of the uterus included both the uterine corpus and the cervix [32].

All pregnant women were divided into two groups: Group I (n = 166) indicated that the placenta was located on the adenomyotic lesion (as shown in Fig. 2a,b); Group II (n = 145) exhibited that the placenta was far away from the adenomyotic lesion (Fig. 2c,d). Compared with group II, diffuse adenomyosis was more common in group I (104 (62.65%) *vs.* 67 (46.21%), p = 0.01), as well as more likely to have concordant endometriosis (53 (31.93%) *vs.* 23 (15.86%), p = 0.002). Considering the age, parity, ART, cases with scarred uterus, history of hormone treatment and pre-pregnancy uterine size, there were no significant differences between group I and group II.

The pre-pregnant uterine size of patients with diffuse adenomyosis was larger than the size of patients with focal adenomyosis in both two groups (the proportion of pre-pregnant uterine size larger than three months gestation, focal *vs.* diffuse: group I 3 (3/62, 4.84%) *vs.* 18 (18/104, 17.31%), p = 0.01; group II 2 (2/78, 2.65%) *vs.* 18 (18/67, 26.87%)).

3.2 Perinatal Outcomes in Both Groups

The results of comparison of perinatal outcomes are detailed in Table 2. Of the 311 cases, 12 (3.86%) cases were diagnosed with cervical incompetence, 45 (14.47%) cases were complicated with PIH, 60 (19.29%) cases were complicated with GDM, and 15 (4.82%) cases were complicated with oligohydramnios. Twenty three (7.40%) cases of FGR and 47 (15.11%) cases of premature rupture of fetal membranes (PROM) were detected. There were 2

cases diagnosed with uterine rupture or threatened uterine rupture with both cases being in group I. The overall rate of preterm delivery was 25.72% (80/311), which was significantly higher in group I than group II (34.94% (58/166) *vs.* 15.17% (22/145), $p < 0.001$). Cephalic presentation was present in 301 (96.78%) cases at birth and 10 cases demonstrated non-cephalic presentation. Cesarean section occurred in 250 (80.39%) cases and 61 (19.61%) cases experienced vaginal delivery. A total of 11 (3.54%) cases experienced fetal distress and there was 1 case of still birth in group I at 23 weeks gestation. The overall median birth weight was 3090 (2580, 3400) g, with a lower weight in group I than group II (3050 (2350, 3335) g *vs.* 3100 (2800, 3415) g, $p = 0.02$). There were 43 (13.83%) women with placenta malposition, including both placenta previa or low-lying placenta. The placenta malposition was more often shown in group I than group II (33 (19.88%) *vs.* 10 (6.90%), $p = 0.002$). Placental abruption occurred in 11 (3.54%) cases. The median placental surface area was 324 (288, 360) cm^2, which was significantly less in group I than group II (323 (256, 360) cm^2 *vs.* 342 (306, 360) cm^2, $p = 0.004$). The median blood loss during delivery was 300 (200, 400) mL. Birth weight played an important role in neonatal outcome. We investigated the relationship between birth weight and placental surface area. Birth weight was positively correlated with placental surface area as shown in Fig. 3 (R = 0.44, $p < 0.05$).

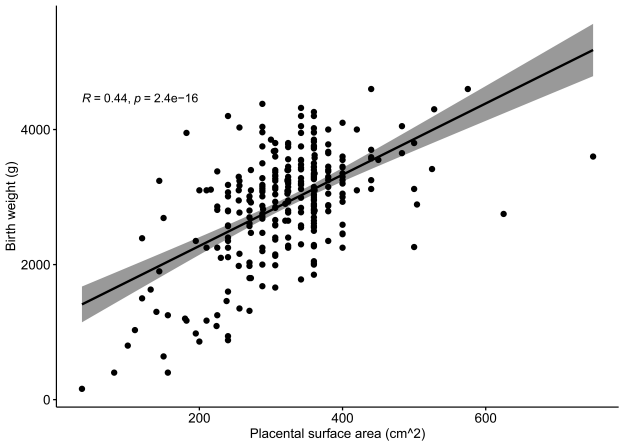

Fig. 3. Spearman correlation analysis showed that the birth weight was positively associated with placental surface area.

There were no significant differences for cervical incompetence, PIH, GDM, oligohydramnios, FGR, PROM, uterine rupture or threatened uterine rupture, fetal presentation, fetal distress, delivery mode, placental abruption and blood loss during delivery between group I and group II.

3.3 Effects of Factors on Neonatal Adverse Outcomes

As shown in Table 3, 5 variables were found to be associated with composite neonatal adverse outcome by mul-

Table 3. Multivariate logistic regression on risk factors of neonatal adverse outcomes.

	OR	95% CI		*p* value
(Intercept)	0.03	0.01	0.14	<0.001
Group				
I (n = 166)	3.13	1.47	7	0.004
II (n = 145)				Reference
ART				
yes (n = 69)	1.44	0.55	3.67	0.45
no (n = 242)				Reference
Age				
≥35 years (n = 155)	1.33	0.62	2.88	0.47
<35 years (n = 156)				Reference
Parity				
Multipara (n = 188)	1.5	0.58	3.96	0.4
Primipara (n = 123)				Reference
Adenomyosis type				
Diffuse (n = 171)	1.54	0.7	3.41	0.29
Focal (n = 140)				Reference
Pre-pregnant enlarged uterus				
yes (n = 41)	0.85	0.31	2.19	0.74
no (n = 270)				Reference
History of endometriosis				
yes (n = 76)	1.25	0.53	2.88	0.6
no (n = 235)				Reference
Cervical incompetence				
yes (n = 12)	1.71	0.18	20.46	0.65
no (n = 299)				Reference
PIH				
yes (n = 45)	3.46	1.39	8.7	0.01
no (n = 266)				Reference
GDM				
yes (n = 60)	0.97	0.35	2.43	0.95
no (n = 251)				Reference
Placenta malposition*				
yes (n = 43)	3.28	1.18	9.22	0.02
no (n = 268)				Reference
Placental abruption				
yes (n = 11)	10.14	2.26	54.44	0.003
no (n = 300)				Reference
Oligohydramnios				
yes (n = 15)	1.96	0.23	12.22	0.49
no (n = 296)				Reference
PROM				
yes (n = 47)	2.41	0.86	6.52	0.09
no (n = 264)				Reference
Delivery mode				
Cesarean delivery (n = 250)	0.73	0.25	2.2	0.56
Vaginal delivery (n = 61)				Reference
Scarred uterus				
yes (n = 133)	2.71	1.17	6.46	0.02
no (n = 178)				Reference

OR, Odds ratio; CI, confidence interval.

*Placental malposition includes placenta previa or low-lying placenta.

Neonatal adverse outcomes includes preterm delivery, FGR and 5 min Apgar <7.

Table 4. Multivariate logistic regression on risk factors of maternal adverse outcomes.

	OR	95% CI		*p* value
Intercept	0.46	0.15	1.36	0.17
Group				
I (n = 166)	0.63	0.35	1.14	0.13
II (n = 145)				Reference
ART				
yes (n = 69)	0.62	0.28	1.34	0.23
no (n = 242)				Reference
Age				
≥35 years (n = 155)	2.03	1.11	3.76	0.02
<35 years (n = 156)				Reference
Parity				
Multipara (n = 188)	1.47	0.7	3.12	0.31
Primipara (n = 123)				Reference
Adenomyosis type				
Diffuse (n = 171)	1.73	0.91	3.32	0.1
Focal (n = 140)				Reference
Pre-pregnant enlarged uterus				
yes (n = 41)	0.59	0.26	1.28	0.19
no (n = 270)				Reference
History of endometriosis				
yes (n = 76)	0.64	0.3	1.32	0.23
no (n = 235)				Reference
Cervical incompetence				
yes (n = 12)	3.34	0.48	28.61	0.22
no (n = 299)				Reference
Placenta malposition*				
yes (n = 43)	2	0.78	5.27	0.15
no (n = 268)				Reference
Oligohydramnios				
yes (n = 15)	0.6	0.08	3.09	0.56
no (n = 296)				Reference
PROM				
yes (n = 47)	0.58	0.24	1.36	0.22
no (n = 264)				Reference
Delivery mode				
Cesarean delivery (n = 250)	1.1	0.47	2.65	0.82
Vaginal delivery (n = 61)				Reference
Scarred uterus				
yes (n = 133)	0.79	0.4	1.53	0.49
no (n = 178)				Reference

*Placental malposition includes placenta previa or low-lying placenta.

Maternal adverse outcomes includes PIH, GDM, uterine rupture or threatened uterine rupture, placental abruption and postpartum hemorrhage.

tivariable logistic regression analysis. Placenta location above the uterine adenomyosis increased the risk of composite neonatal adverse outcome (odds ratio (OR): 3.13, 95% confidence interval (95% CI): 1.47–7.00, $p = 0.004$). There were 4 other risk factors related to composite neonatal adverse outcome, including PIH (OR: 3.46, 95% CI: 1.39–8.70, $p = 0.01$), placenta malposition (OR: 3.28, 95% CI: 1.18–9.22, $p = 0.01$), placenta abruption (OR: 10.14, 95% CI: 2.26–54.44, $p = 0.003$) and scarred uterus (OR: 2.71, 95% CI: 1.17–6.46, $p = 0.02$). Moreover, searman correlation analysis demonstrated that the birth weight was positively associated with placental surface area (R = 0.44, $p < 0.001$), as shown in Fig. 3.

Table 5. Multivariate logistic regression on risk factors of placenta exists above adenomyosis.

	OR	95% CI		*p* value
Intercept	0.64	0.45	0.91	0.01
Adenomyosis type				
Diffuse (n = 171)	1.72	1.08	2.74	0.02
Focal (n = 140)				Reference
History of endometriosis				
yes (n = 76)	2.07	1.18	3.71	0.01
no (n = 235)				Reference
Placenta malposition*				
yes (n = 43)	2.63	1.25	5.92	0.01
no (n = 268)				Reference

*Placental malposition includes placenta previa or low-lying placenta.

3.4 Effects of Factors on Maternal Adverse Outcomes

As shown in Table 4, placenta location above the uterine adenomyosis showed no significant effect on the risk of composite maternal adverse outcomes; however, the maternal age older than 35 years might increase the risk (OR: 2.03, 95% CI: 1.11–3.76, $p = 0.02$).

3.5 Effects of Factors on Placenta Existing above Adenomyosis

As shown in Table 5, 3 variables were found to be associated with placenta location above the uterine adenomyosis by multivariable logistic regression analysis. Diffuse adenomyosis (OR: 1.72, 95% CI: 1.08–2.74, $p = 0.02$), endometriosis history (OR: 2.07, 95% CI: 1.18–3.71, $p = 0.01$) and placenta malposition (OR: 2.63, 95% CI: 1.25–5.92, $p = 0.01$) might increase the risk of placenta implantation site overlapping the uterine adenomyosis.

4. Discussion

Recent publications have confirmed that adenomyosis was associated with increased risks of early miscarriage, second trimester miscarriage, preterm delivery, preeclampsia, FGR, placental malposition, postpartum bleeding, cesarean section rate and the incidence of pregnancy by ART [33–35]. In addition, the gestational age and neonatal birth weight at delivery were significantly lower than those of pregnant patients without adenomyosis and the placental attachment on the area of adenomyotic lesion could be associated with FGR [13,25].

Our study drew similar conclusions and reconfirmed the conclusion that the relationship between placental implantation site and adenomyotic lesion location had a substantial impact on pregnancy outcome of adenomyosis patients [29]. In our study, the placenta implantation site

above the uterine adenomyosis had a high correlation with preterm delivery, lower birth weight and placenta malposition. However, the incidence of FGR showed no significant difference.

Adenomyosis-associated lower neonatal birth weight and preterm delivery were thought to have a pathophysiological correlation with inflammation, free radicals and junctional zone alterations. Specifically, thickening of the myometrial junctional zone was the typical change noted in adenomyosis patients by magnetic resonance imaging (MRI). Placental dysplasia caused by impaired remodeling of spiral arteries in this area creates a hostile environment for the placenta that impedes adequate fetal exchange with the maternal blood supply, possibly through a vascular steal mechanism, leading to numerous adverse pregnancy complications [16,36–39]. Previous studies have suggested that fetuses with lower placental weight and smaller placental surface area were at higher risk of developing FGR [40,41], a finding in accordance with the results of our study that birth weight was positively associated with placental surface area. The lower birth weight in women with placenta location overlapping adenomyosis may be related to the smaller placenta being caused by the adenomyosis.

Adenomyosis is also an independent risk factor for impaired reproductive function [42]. These patients have a higher incidence of infertility and the clinical pregnancy rate of assisted reproductive technology in adenomyosis patients is significantly reduced [36]. In our study, 69 cases (22.19%) underwent ART, with the percentage being much higher when compared with average women. Moreover, researchers have found that the adverse pregnancy outcome of patients whose pregnancy was complicated with adenomyosis was closely related to the severity of the disease and whether it was diffuse adenomyosis [43,44]. A clinical trial from Japan recruited 272 pregnant women with adenomyosis and reported that the rates of miscarriage (>12 weeks) and cervical incompetency were positively related to the size of the adenomyosis, and that the rates of PIH and uterine infection in patients with diffuse adenomyosis were higher than that in patients with focal adenomyosis [45]. As related to whether the adenomyosis was surgically or medically treated prior to pregnancy, the rates of pregnancy complications did not differ to a statistically significant extent [45]. Another Japanese study of 325 pregnant women with adenomyosis (136 with co-existing endometriosis) demonstrated that the frequency of obstetric complications was as high as 60.0% and only pregnant women with a medical history of adenomyosis experienced adverse events of mild preeclampsia, placental abruption and FGR (adjusted odds ratio (aOR) = 1.86, aOR = 2.62, and aOR = 2.72, respectively) [46].

Although it is currently believed that the adverse pregnancy outcomes of adenomyosis patients are related to the severity and lesion type of adenomyosis [43,44], the exact mechanism leading to the phenomenon is still unclear. Thickening of the myometrium and endometrial-myometrial junction, elevated inflammatory cytokines, such as IL-6 and TNF-α, could lead to insufficient infiltration of trophoblast cells into the endometrium, leading to poor remodeling of the spiral artery and placental dysplasia, resulting in a small placenta and FGR [47–51]. Further investigations are needed to better understand the pathophysiologic mechanisms of the spectrum of adenomyotic lesion location-associated obstetric complications. Despite the low level of evidence, pregnant women with diffuse adenomyosis should be considered at high risk for adverse obstetric outcomes. The characteristics of adenomyosis affect the blood supply of the mother and fetus, which may be the main reason for the adverse outcomes of pregnancy [52]. Recently, Ono *et al*. [29] reported that the relationship between placental location and lesion location in pregnant patients complicated with adenomyosis markedly affected perinatal outcomes. The incidence of adverse perinatal outcomes such as FGR in patients with the placenta very close to or directly implanted on the adenomyotic lesion was significantly higher than that in patients with placenta far away from the lesion.

Our study retrospectively analyzed the clinical data of 311 pregnant patients complicated with adenomyosis. Our data demonstrated that the placental implantation site was closely related to pregnancy outcomes. If the placenta was located on or close to the adenomyotic lesion, the rate of preterm delivery and placental malposition were significantly increased, and the gestational age, neonatal birth weight and placental size were significantly decreased, which were consistent with the results reported in the literature [13,53]. Thus, it was further confirmed that there were severe adverse pregnant outcomes in adenomyosis patients whose placenta was closely implanted to the lesion.

Our study detected that diffuse adenomyosis, endometriosis history and placenta malposition might increase the risk of placenta implantation site overlapping the uterine adenomyosis, this pathological mechanism needs to be further explored. This indicates that patients with adenomyosis are recommended to evaluate the severity and lesion type of adenomyosis before pregnancy, and offer early intervention, especially for those women co-existing with an endometriosis history. Once the patient is pregnant, ultrasound and other imaging techniques such as MRI should be utilized to identify the relationship between the embryo implantation site and the lesion position of adenomyosis, and to check the uterine artery pulsation index, in order to closely monitor and intervene when appropriate. An early intervention is the usage of aspirin, in order to prevent early placental dysplasia, including PIH [54] and recurrent miscarriage [55]. The study of Yamanaka [56] revealed that adenomyosis had a risk of activating the blood coagulation system and increased the risk of thrombosis, suggesting that aspirin be considered to be useful in pregnancy complicated by adenomyosis.

Our study determined that severe adverse pregnant outcomes in adenomyosis patients were closely related to the placenta implantation site if it was overlapping lesion. These conclusions are consistent with those reported by Ono *et al*. [29]. Due to the difficulty to distinguish junctional zone (JZ) in the pregnant uterus by ultrasound screening, it is hard for us to determine the relationship between adenomyosis lesion and JZ, as well as the exact distance between the placenta and the lesions. Thus, our recommendation is that pregnant patients complicated with adenomyosis should undergo MRI in late pregnancy to identify the relationship between placental implantation site and lesion location, uterine artery pulsation index and fetal growth.

In our study, there was no significant difference in the incidence of FGR and PIH, regardless of the location of the placenta. Other researchers have found that PIH was a maternal complication related to an autoimmune mechanism, so it might have something to do with immune pathogenesis of adenomyosis [57]. Although other literature reported that the incidence of FGR in pregnant patients complicated with adenomyosis was mainly related to diffuse adenomyosis [52], our data showed no difference, which might due to one of the limitations of the study (the relatively small number of cases and imperfect retrospective data). There are still other limitations. The history of cesarean section and ART may be associated with the risk of maternal and neonatal outcomes but these cases were not excluded from the study. Fortunately, the patients with the history of cesarean section or ART were symmetrically distributed in two groups. Furthermore, all patients merely had ultrasound images without MRI images since our study was a retrospective approach, so the specific data of the distance between the placental implantation site and the lesion of adenomyosis could not be acquired. Obviously, it is necessary to further comprehensively apply ultrasound and MRI to classify the types of adenomyosis, measure the size of uterus, evaluate the severity of the disease, measure the distance between the placental implantation site and the lesion, and implement a multicenter prospective study with a large sample size to evaluate the adverse pregnancy outcomes of pregnant patients complicated with adenomyosis.

5. Conclusions

Pregnant women whose pregnancy is complicated by adenomyosis are associated with adverse pregnancy outcomes. When the placental implantation site overlaps the adenomyotic lesion, adverse pregnancy outcomes are more likely to occur, and include preterm delivery and lower birth weight. Women with diffuse adenomyosis, endometriosis history and placenta malposition are more likely to have placental implantation site overlapping the adenomyotic lesion. Therefore, patients with adenomyosis need detailed and thorough evaluation prior to pregnancy. Imaging examinations should be performed during the pregnant process to determine the placental implantation site, uterine artery pulsation index and fetal growth. Close monitoring and early intervention such as consultant-led care when clinically appropriate should be carried out to improve pregnancy outcomes.

Availability of Data and Materials

The data and materials generated during and analyzed during the present study are available from the corresponding author upon reasonable request.

Author Contributions

XZ and PX designed the research study. PX, XH, YZ, YW and GZ performed the research. PX, XH, JW analyzed the data. PX, JW and XZ wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of Women's Hospital, School of Medicine, Zhejiang University (No. IRB-20210310-R). All patients were exempt from informed consent because this study was retrospective.

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Conflict of Interest

The authors declare no conflict of interest.

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