European Review for Medical and Pharmacological Sciences 2024; 28: 577-583

Impact of adenomyosis on pregnancy outcomes: a retrospective consecutive cohort study

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Abstract. – OBJECTIVE: This retrospective study explored the potential connection between adenomyosis and pregnancy outcomes.

PATIENTS AND METHODS: A study included data from a total of 1,208 pregnancies. The adenomyosis group included 334 pregnant women with adenomyosis, and women in the control group (n=874) had uncomplicated pregnancies. Data on pregnancy complications and maternal and neonatal outcomes were compared.

RESULTS: The incidence of gestational hypertension, gestational diabetes, and placenta previa was higher in the adenomyosis group compared to the control group ($p<0.05$). Adenomyosis was linked to a higher risk of postpartum hemorrhage (1,000-1,500 ml) but a lower risk of premature rupture of membranes (PROM) ($p<0.05$). Diagnosis of adenomyosis correlated with increased incidence of low fetal weight (20.3% *vs.* 21.3%, $p<0.05$) and a low APGAR score at 1 min ($p<0.05$).

CONCLUSIONS: Adenomyosis correlated with a higher incidence of gestational hypertension, placenta previa, and gestational diabetes. At the same time, adenomyosis correlated with a significantly lower incidence of PROM compared to uncomplicated pregnancy. There was a significant increase in the incidence of postpartum hemorrhage and a higher risk of low fetal weight and lower APGAR score at 1 min in pregnancies with adenomyosis.

Key Words:
Adenomyosis, Pregnancy outcomes, Obstetrical complications, Obstetrics, Neonatal outcomes.

Introduction

Adenomyosis affects approximately 20-35% of women of childbearing age[1]. Recent developments in assisted reproductive technology and imaging diagnostic methods have led to a stable rise in the number of women diagnosed with adenomyosis[2-4].

Multiple studies[5,6] suggest that adenomyosis may affect the physiological process of pregnancy and may cause obstetric complications, such as preeclampsia, hypertension in pregnancy (HDP), premature rupture of membranes (PROM), gestational diabetes mellitus (GDM), premature delivery, small-for-gestational-age (SGA) fetal status, intrahepatic cholestasis of pregnancy (ICP), etc. Previous studies[7] have also suggested that the depth and number of invasions of adenomyosis lesions are significantly associated with adverse pregnancy outcomes. Deeper invasions or greater numbers of lesions correlate with increased rates of adverse pregnancy outcomes and lower rates of successful pregnancy to delivery. However, to our knowledge, there are still relatively few systematic studies exploring the correlation between adenomyosis and pregnancy outcomes.

The aim of the current retrospective and consecutive cohort study is to assess a potential link between adenomyosis and pregnancy outcomes.

Patients and Methods

Patients and Grouping

Medical records of 1,208 pregnant women at the Fujian Provincial Maternity and Children's Hospital, China, collected between July 2016 and December 2020, were included. All women carried their pregnancies to at least 28 completed weeks of gestation and underwent cesarean section. Of 1,208 women, 334 had adenomyosis (adenomyosis group), and 874 had uncomplicated pregnancies (control group). Institutional Ethics Committee of Fujian Provincial Maternity and Children's Hospital

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(2021KRD031) approved the study. Guidelines of the Declaration of Helsinki were followed to protect rights of all participants. Informed consent was waived for the retrospective study. A flow chart of the study design is presented in Figure 1.

Inclusion criteria: age ≥18 years, cesarean section, postoperative diagnosis of adenomyosis (microscopic evidence of island-like distribution of ectopic endometrial glands and stroma in the muscular layer[8]). The Exclusion criteria: unconsciousness or a state of severe disease, learning and mental impairment, detected major fetal abnormalities.

Outcome Measurements

Pregnancy and delivery data, gestational age (weeks), gravidity, parity, neonatal and placental weight, volume of bleeding, HDP, PROM, postpartum hemorrhage (PPH), GDM, ICP, placental abruption, hemolysis, raised levels of liver enzymes, and low platelet (HELLP) syndrome, and SGA.

GDM diagnosis was based on the National Health and Family Planning Commission of the People's Republic of China guidelines.

Diagnostic Criteria

HDP: systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg. HDP was further classified as gestational or chronic hypertension, pre-eclampsia on top of chronic hypertension, pre-eclampsia, or eclampsia[9,10]. Proteinuria ≥ 1+, accompanied by elevated blood pressure and lack of urinary tract infection.

PROM: evidence of amniotic fluid leaking and pooling, a basic vaginal fluid pH, and microscopic evidence of arborization.

ICP: new-onset pruritus, accompanied by a total bile acid level of >10 μmol/l in the absence of liver disease.

HELLP syndrome: hemolysis (serum lactate dehydrogenase (LDH) >600 IU/L; bilirubin >1.2 mg/dL; schistocytes in peripheral blood), elevated serum alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >70 IU/L and platelet count <100,000/mm^3.

Placental abruption: abdominal pain, vaginal bleeding, uterine contractions, fetal distress, and abnormal vital sign.

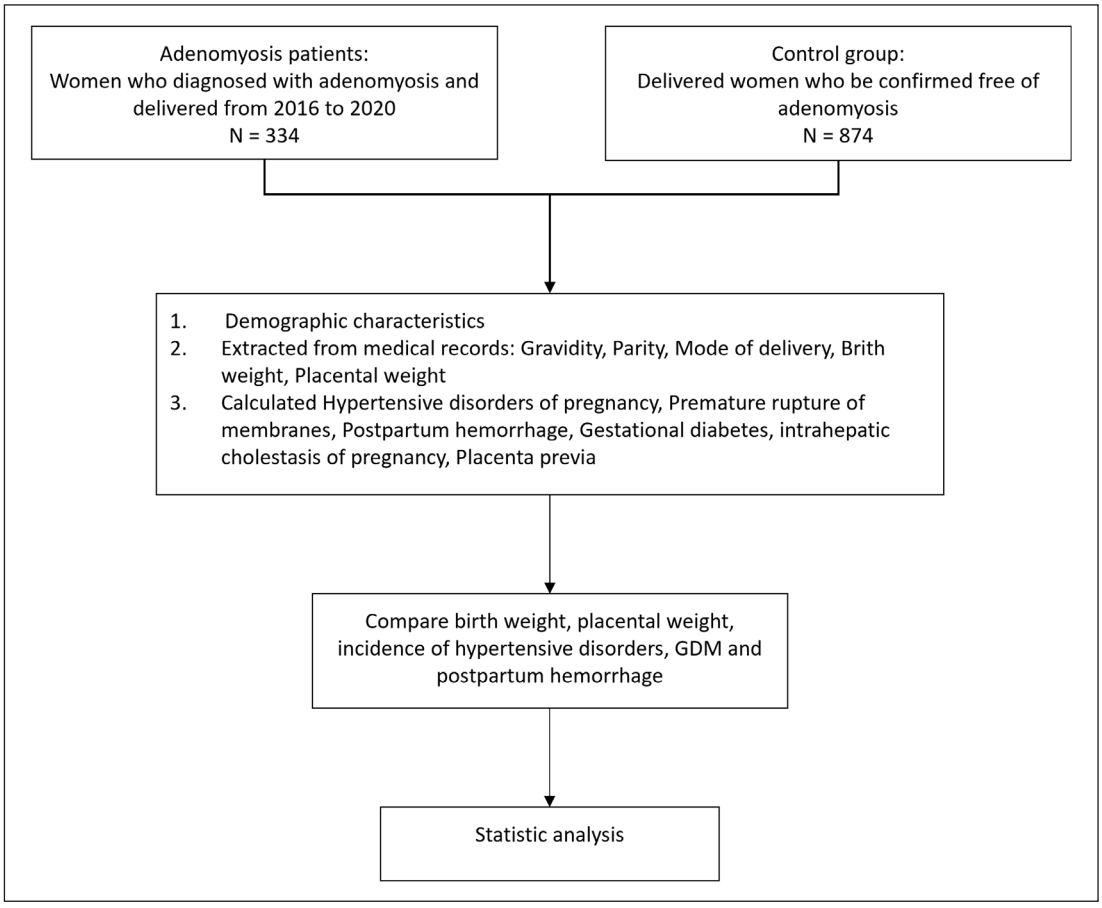

Figure 1. Study flow chart.

Statistical Analysis

SPSS 19.0 (IBM Corp., Armonk, NY, USA) was used. Continuous data were shown as means±standard deviation (SD), with independent *t*-test or a Kruskal-Wallis test. Dichotomous data were shown as percentages and χ^2 test or Fisher's exact test were used. $p<0.05$ was statistically significant. For dichotomous outcomes, relative and absolute risk differences with 95% (CI) were evaluated by Fisher's exact test.

Results

Of 1,208 eligible women, 334 women were included in the adenomyosis group, and 874 women in the control group. Baseline data are summarized in Table I. Women in the adenomyosis group were slightly older (35.38±4.41 *vs.* 31.68±4.35 in the control group, $p=0.394$). Gestational weeks at the time of termination of pregnancy were comparable in both groups (37.87±2.71 *vs.* 37.99±2.19, $p=0.436$). In terms of reproductive history, the proportion of primipara was significantly lower (25.7% *vs.* 40.50%, $p<0.001$), and the number of multigravidas was significantly greater in the adenomyosis group (74.3% *vs.* 59.5%, $p<0.001$).

Table II demonstrates the differences in pregnancy complications between the groups. We found a significantly greater prevalence of gestational hypertension (5.69% *vs.* 2.29%, $p=0.004$), GD (33.84% *vs.* 27.69%, $p=0.04$), placenta previa (4.5% *vs.* 2.2%, $p=0.029$) in the adenomyosis group. However, prevalence of preeclampsia, chronic hypertension, chronic hypertension complicated by preeclampsia and HELLP syndrome in both groups were comparable (2.1% *vs.* 3.1%, $p=0.35$; 0.3% *vs.* 0.8%, $p=0.572$; 0 *vs.* 0.6%, $p=0.331$; 0 *vs.* 0.2%, $p=1.0$, respectively). Similarly, the incidence of functional cholestasis was comparable (0.90% *vs.* 1.3%, $p=0.824$). The prevalence of PROM was significantly greater in the control group (15.3% *vs.* 20.4%, $p=0.043$).

The overall incidence and the volume of PPH were significantly higher in the adenomyosis group (Table III), with nearly half of the patients diagnosed with adenomyosis presenting with a blood loss of over 2000 ml (2.4% *vs.* 1.03%, $p=0.017$).

Table IV shows fetal and neonatal outcomes in both groups. Adenomyosis correlated with a significantly higher incidence of low-weight (2,500-2,999g) neonates (20.3% *vs.* 21.3%, $p=0.027$) and significantly lower APGAR score at 1 minute ($p=0.04$). Incidence of preterm delivery, placental

Table I. Baseline characteristics of adenomyosis and the control group.

Baseline characteristics	Adenomyosis (%) n=334	Control group (%) n=874	*p*-value
Maternal age (years, average ±S/D)	35.38±4.41	31.68±4.35	0.394
Gestational age (weeks, average ±S/D)	37.87±2.71	37.99±2.19	0.436
Gravidity			
=1	86 (25.7)	354 (40.50)	<0.001
>1	248 (74.3)	520 (59.50)	
Parity			
=1	136 (39.53)	496 (56.75)	<0.001
>1	198 (57.56)	378 (43.25)	

Table II. Gestational complications of adenomyosis and the control group.

Gestational complications	Adenomyosis (%) n=334	Control group (%) n=874	*p*-value
Hypertensive disorders of pregnancy	15 (4.5)	36 (4.1)	0.774
Gestational hypertension	19 (5.69)	20 (2.29)	0.004
Preeclampsia	7 (2.1)	27 (3.1)	0.350
Chronic hypertension complicating pregnancy	1 (0.3)	7 (0.8)	0.572
Preeclampsia superimposed upon chronic hypertension	0	5 (0.6)	0.331
HELLP syndrome	0	2 (0.2)	1.000
Premature rupture of membranes	51 (15.3)	178 (20.4)	0.043
Postpartum hemorrhage	8(2.4)	9 (1.03)	0.017
Gestational diabetes	113 (33.83)	242 (27.69)	0.04
Intrahepatic cholestasis of pregnancy	3 (0.90)	11 (1.3)	0.824
Placenta previa	15 (4.5)	19 (2.2)	0.029

weight, or 5-minute APGAR scores for newborns in both groups were comparable.

Discussion

Our results showed that adenomyosis is linked to an increased incidence of pregnancy complications such as gestational hypertension, GD, and placenta previa. Diagnosis of adenomyosis was linked to lower birth weight of neonates, higher rates of PPH and higher volume of blood loss.

HDP is a group of pregnancy-related multi-system disorders that include gestational hypertension, pre-eclampsia and eclampsia[7]. Several studies showed that the prevalence of gestational hypertension and pre-eclampsia is higher in pregnancies complicated with adenomyosis. However, our results showed this correlation only in terms of gestational hypertension. This may be due to the higher gestational hypertension awareness in our hospital. Timely treatment of gestational hypertension allows for a reduction in the incidence of preeclampsia and eclampsia.

Our study showed an association of adenomyosis with GDM. Only a few studies[11-13] reported on the incidence of gestational diabetes in association with adenomyosis, with conflicting results. A multicenter case-control study by Shinohara et al[11] that included 61 patients with adenomyosis did not find a significant correlation of GDM and adenomyosis (p=0.15). A retrospective case-control study by Hashimoto et al[13] included 49 women with adenomyosis and 245 women with uncomplicated pregnancies and showed a higher risk in the control group (OR 0.11; 95% CI 0.02-0.85). However, these studies[11,13] had relatively small sample sizes. Harada et al[12] conducted a large prospective cohort study that included 96,655 women (of them 345 with adenomyosis) and showed a higher (p=0.023) incidence of GDM in this cohort. Our results agree with this observation. Insulin resistance is the main contributor to the pathophysiology of GDM. Recent studies[9] emphasized the importance of a low-level inflammatory state in the pathogenesis of insulin resistance. We may speculate that since adenomyosis is a chronic inflammatory disease, inflammatory and immune processes in the uterus of patients with adenomyosis may contribute to the higher incidence of GDM.

During pregnancy, placenta supplies the fetus with oxygenated blood *via* the spiral arteries 10, and impaired placentation is linked to a number of adverse pregnancy and neonatal outcomes due to

Table III. Amount of bleeding in adenomyosis and the control group.

Amount of bleeding (ml)	No (%) of PPH		p-value
	Adenomyosis (%) n= 334	Control group (%) n=874	
1000-	5 (1.5)	7 (0.8)	
1500-	0	0	
2000-	3 (0.90)	1 (0.1)	
2500-	0	0	
3000-	0	1 (0.1)	
Total	8 (2.40)	9 (1.03)	0.017

PPH=postpartum hemorrhage.

Table IV. Fetal and neonatal outcomes of adenomyosis and control group.

Fetal and neonatal outcomes	Adenomyosis (%) n= 334	Control group (%) n=874	p-value
Birth weight (g)			
<2,500	39 (11.8)	118 (13.5)	0.206
2,500-2,999	67 (20.3)	186 (21.3)	0.027
3,000-3,499	129 (39.1)	313 (35.8)	0.367
3,500-3,999	77 (23.3)	214 (24.5)	0.877
≥4,000	18 (5.5)	43 (4.9)	0.788
Placental weight (g, average ±S/D)	656.54±142.06 (12.9)	667.9±193.51 (15.3)	0.335
Preterm birth	5 (1.5)	8 (0.9)	0.280
APGAR≤7 at 1 min	5 (1.5)	7 (0.8)	0.040
APGAR≤7 at 5 min	0	1 (0.1)	1.000

placental insufficiency and disturbed uterine environment6. Studies[10,13] show the connection between adenomyosis and adverse placental function, such as placental abruption, preterm PROM, and placental malposition. In agreement with these reports, our results demonstrated that adenomyosis correlated with elevated rates of placenta previa.

Interestingly, PROM incidence was significantly lower in the adenomyosis group compared to normal pregnancy. We may speculate that this inconsistency with the previous results may be explained by the link between the rate of PROM and the severity of adenomyosis. Additionally, many pregnant women with adenomyosis are older and have a high rate of assisted reproductive technology (ART) use, which may also impact the rate of this complication. Our results may have clinical implications since they suggest that the diagnosis of adenomyosis alone is not enough to correctly estimate the risk of this potential complication, and factors such as age, severity of adenomyosis, or use of ART need to be considered. Our observations should be further validated by additional studies that may also identify other factors impacting the risk of PROM in women with adenomyosis.

Another significant finding of our study was the link between the incidence of postpartum hemorrhage and adenomyosis. PPH is accountable for about 1/4 of all cases of maternal mortality each year[14]. Its probability is estimated at 5-22%[15] and has been increasing over the past few decades. The possible mechanisms of this association are complex. Adenomyosis can lead to changes in the endometrium and inner muscle layer, largely due to the remodeling of the uterine spiral artery[16]. Recent studies[15] showed that adenomyosis leads to structural changes in the myometrial junctional zone (JZ), resulting in altered decidualization and early placentation. This, in turn, leads to incomplete placenta and placenta retention, affecting the contractile force of the muscular layer, which may result in PPH[17]. Additionally, adenomyosis is associated with changes in angiogenesis. Physiologically, angiogenesis occurs monthly in the proliferative period of the menstrual cycle. The process of neovascularization is relatively fragile and easy to damage[6]. Adenomyosis also correlates with a decrease in the contractile force of the myometrium. Patients with adenomyosis have hypertrophy of muscle cells and nuclei and poor contractile ability. As a result, placental attachment cannot contract completely after the delivery, which can easily lead to PPH[18].

Several studies[19] focused on the impact of adenomyosis on pregnancy outcomes. Diffuse adenomyosis in pregnant women strongly correlated with SGA neonates, and partial remodeling of the myometrial spiral arteries or defective deep placentation correlated with a variety of adverse maternal and neonatal outcomes[20-22]. Similar to these studies, our results showed an association of adenomyosis with a significantly higher incidence of low-weight (2,500-2,999 g) neonates (20.3% *vs.* 21.3%, p=0.027), and lower APGAR score at 1 min (p=0.04).

Limitations

Our study has some limitations. This is retrospective single-center study, which may impact the robustness and generalizability of our results. Additionally, we did not account for parameters such as the severity of adenomyosis, age, or use of ART. Further multi-center trials are needed to validate our results and to identify other factors that may affect the rate of adverse pregnancy outcomes in pregnancies with adenomyosis.

Conclusions

Our results show that adenomyosis is linked to an increased incidence of gestational hypertension, placenta previa, and gestational diabetes. In terms of neonatal outcomes, adenomyosis correlates with increased rates of low fetal weight and low APGAR score at 1 minute. Additionally, adenomyosis correlates with an increase in the incidence of postpartum hemorrhage, especially in the 1,000 ml to 1,500 ml range. The incidence of PROM was lower in the adenomyosis group, suggesting that the diagnosis of adenomyosis alone is not enough to correctly estimate the risk of PROM. Our observations provide a valuable reference for clinicians to timely manage blood pressure and glucose levels in pregnant women with adenomyosis and monitor for potential complications, such as postpartum hemorrhage.

Funding

This research study was supported by grants from the Natural Science Foundation of Fujian Province, China (2021J01414), and the Provincial special subsidy for the health of the Fujian Provincial Department of Finance (2100206-5052-302).

Availability of Data and Materials

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

Authors' Contributions
LC and XC conceived and designed the study. JS, YZ, XX, SL, XZ, HY and Yulong Zhang collected the data and performed the analysis. LC and XC were involved in the manuscript's writing. All authors have read and approved the final manuscript.

Ethics Approval
The study was approved by the Institutional Ethics Committee of Fujian Provincial Maternity and Children's Hospital (2021KRD031) and conducted according to the guidelines of the Declaration of Helsinki.

Informed Consent
Not applicable.

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

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