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Adenomyosis as a Potential Risk Factor for Adverse Pregnancy Outcomes: A Multicenter Case-Control Study

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As the number of women who postpone their first pregnancy until their late 30s or early 40s is increasing, adenomyosis is more frequently encountered by obstetricians. Some studies have reported on the relationship between adenomyosis and pregnancy complications. We aimed to investigate the effect of adenomyosis on pregnancy complications and outcomes and associations between adenomyosis type and pregnancy outcomes. This multicenter retrospective 1:4 case-control study included 61 women with singleton pregnancies diagnosed with adenomyosis. The control group included women with singleton pregnancies without adenomyosis; these women were matched to those with adenomyosis using propensity scores. The incidence of obstetric complications, delivery, and neonatal outcomes were compared. The adenomyosis group (n = 61) had significantly higher incidence of preterm delivery (21.3% vs. 9.4%), hypertensive disorders of pregnancy (13.1% vs. 5.3%), cesarean delivery (46.0% vs. 20.9%), and postpartum hemorrhage (57.3% vs. 36.8%) than the control group (n = 244). Subgroup analysis by the adenomyosis type revealed that the diffuse adenomyosis group (n = 41) was significantly more likely to experience preterm labor (29.3% vs. 7.3%), hypertensive disorders of pregnancy (17.0% vs. 5.5%), severe hypertensive disorders of pregnancy (12.2% vs. 1.8%), preterm premature rupture of membranes (12.2% vs. 2.4%), cesarean delivery (61.3% vs. 18.9%), and postpartum hemorrhage (70.7% vs. 44.5%) than the control group (n = 164). The focal adenomyosis (n = 20) group was not statistically different from the control group (n = 80) with respect to obstetric complications. Women with diffuse adenomyosis require more careful perinatal management than previously thought.

Keywords: adenomyosis; hypertensive disorders of pregnancy; postpartum hemorrhage; pregnancy outcome; preterm labor
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Introduction

Adenomyosis is defined as the presence of endometrial glands and stroma deep within the myometrium. Most patients with adenomyosis are diagnosed in the fourth and fifth decades of life (Kunz et al. 2007). However, as the number of women who are postponing their first pregnancy until their late 30s or early 40s is increasing, adenomyosis is being more frequently encountered by obstetricians. Moreover, the number of pregnancies complicated by adenomyosis has increased because of advanced infertility treatments (Kunz et al. 2007; Harada et al. 2016). A limited number of studies have reported an increased risk of preterm delivery (Juang et al. 2007; Mochimaru et al. 2015; Tamura et al. 2017; Hashimoto et al. 2018), preterm premature rupture of membranes (pPROM), fetal growth restriction (Mochimaru et al. 2015; Hashimoto et al. 2018), hypertensive disorders of pregnancy (HDP) (Mochimaru et al. 2015; Tamura et al 2017; Hashimoto et al. 2018), placental malposition (Hashimoto et al. 2018), and fetal malpresentation (Mochimaru et al. 2015). However, these studies had the following limitations: (1) small sample size; (2) single-center setting or tertiary care setting; (3) inconsistent population between the case and control groups; and (4) inability to prove causality because of the use of descriptive research.

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Adenomyosis can be classified into the following two categories: (1) diffuse adenomyosis, the extensive form of the disease characterized by foci of endometrial mucosa scattered throughout the uterine musculature; and (2) focal adenomyosis, in which the area of the hypertrophic and distorted endometrium and myometrium is restricted (Byun et al. 1999; Bergeron et al. 2006; Tamura et al. 2017). However, little attention has been paid to the association between the specific type of adenomyosis and pregnancy outcomes.

Therefore, we performed a multicenter case–control study to clarify the potential adverse effects of adenomyosis on pregnancy and to improve perinatal prognosis. The primary objective of this multicenter case-control study was to investigate the effect of adenomyosis on pregnancy complications and outcomes. Our secondary objective was to analyze the association between the type of adenomyosis and pregnancy outcomes.

Materials and Methods

Study design and population

In this case–control study, data on women with singleton pregnancies who delivered after 22 weeks' gestation and had adenomyosis were obtained from the records at the University of Yamanashi Hospital, Yamanashi Prefectural Hospital, Kofu Municipal Hospital, Kofu-Kyoritsu Hospital, National Hospital Organization Kofu National Hospital, and Fujiyoshida Municipal Medical Center between January 2008 and February 2019. Magnetic resonance imaging (MRI) and transvaginal ultrasonography (USG) are highly accurate diagnostic tools for detecting adenomyosis (MRI: sensitivity, 70.0-89.0%; specificity, 86.0-92.5%, transvaginal USG: sensitivity, 72.0-86.0%; specificity, 81.0-92.8%) (Reinhold et al. 1996; Bazot et al. 2001; Champaneria et al. 2010). The inclusion criteria for adenomyosis consisted of obvious uterine enlargement and the presence of specific features on MRI or transvaginal USG before or early in pregnancy.

The MRI criteria for diagnosing adenomyosis included (1) a myometrial mass with indistinct margins of primarily low signal intensity or (2) diffuse or focal thickening of the junctional zone with formation of an ill-defined area of low signal intensity on T2-weighted images (Dueholm and Lundorf 2007; Hashimoto et al. 2018). The transvaginal USG criteria for diagnosing adenomyosis included (1) myometrial anterior-posterior asymmetry and/or (2) thickening of the anterior and posterior myometrial walls, with either increased or decreased echogenicity (Bazot et al. 2001; Hashimoto et al. 2018). In addition to these criteria, the transvaginal USG criteria for diagnosing diffuse adenomyosis included no distinction of the endometrial-myometrial junction and subendometrial myometrial striations (Hanafi 2013). The transvaginal USG criteria for diagnosing focal adenomyosis included focal area of myometrical thickening, which presented as a heterogeneous mildly echogenic focal nodule with indistinct margins and cystic spaces (Sakhel and Abuhamad 2012).

Patients with a coexisting uterine myoma were included if they satisfied the aforementioned diagnostic criteria for adenomyosis. Transvaginal USG findings were used to identify the type (focal or diffuse) of uterine adenomyosis based on a previous study that reported that non-invasive diagnosis of adenomyosis was possible with sufficiently high accuracy using both transvaginal USG and MRI and that the difference in accuracy between the two methods was not significant (Champaneria et al. 2010). Additionally, MRI is less widely available, more expensive, and not well-tolerated by all patients compared to USG. In this study, MRI was performed in only six patients.

The control group was selected from among 2,331 women who did not meet the exclusion criteria (a history of surgery for uterine myoma or adenomyosis, uterine malformation, and multiple gestations), underwent transvaginal USG in the first trimester, and were confirmed to be free of adenomyosis with uterine enlargement. These women were randomly selected from those with singleton pregnancies who delivered after 22 weeks' gestation at the University of Yamanashi Hospital, Yamanashi Prefectural Hospital, Kofu Municipal Hospital, Kofu-Kyoritsu Hospital, National Hospital Organization Kofu National Hospital, and Fujiyoshida Municipal Medical Center between January 2008 and February 2019. In particular, when selecting each participant for the control group from among the 2,331 women, we used propensity score (PS) matching to adjust for potential confounders, including maternal age at delivery, parity, and use of assisted reproductive technology (ART), because these factors have been shown to be confounding factors for several obstetric complications (Shevell et al. 2005; Takemura et al. 2013; Toshimitsu et al. 2014). For this study, the following three control groups were set up: control A, for which 61 pregnant women complicated with adenomyosis; control B, for which 41 pregnant women complicated with diffuse adenomyosis; and control C, for which 20 pregnant women complicated with focal adenomyosis.

All procedures in this study were conducted in accordance with the ethical standards of the Human Subjects Review Committees of the University of Yamanashi Hospital (reference number: 1881) and in conformance with the guidelines of the Declaration of Helsinki, as revised in Tokyo 2004. The study protocol was reviewed and approved by the Human Subjects Review Committees of the University of Yamanashi Hospital, Yamanashi Prefectural Hospital, Kofu Municipal Hospital, Kofu-Kyoritsu Hospital, National Hospital Organization Kofu National Hospital, and Fujiyoshida Municipal Medical Center. Informed consent was not obtained from patients owing to the retrospective study design, and patient anonymity was preserved. However, patients were provided with the opportunity to refuse the use of their data through the university's website.

Data collection and definitions of variables

The baseline demographic data were collected from the medical records of the aforementioned six hospitals. The demographic and medical data included maternal age at delivery, pregestational weight, gestational age, parity, delivery method (vaginal or cesarean delivery), and use of ART (*in vitro* fertilization or intracytoplasmic sperm injection). In addition, HDP, preterm delivery, cesarean delivery, gestational diabetes mellitus (GDM), pPROM, placental malposition, fetal malpresentation, postpartum hemorrhage (PPH), and small for gestational age (SGA) infants were considered obstetric complications. Gestational age was determined based on the mother's last menstrual period. If gestational age according to the mother's last menstrual period differed from that determined based on USG at < 11 weeks by more than 7 days, the latter was used to calculate gestational age.

When we compared the frequency of cesarean delivery, we excluded cesarean deliveries performed owing to a previous cesarean delivery or previous uterine surgery in the case and control groups because in such cases, cesarean deliveries were performed with or without perinatal complications. HDP was defined as blood pressure ≥ 140/90 mmHg on at least two occasions during pregnancy (Ohkuchi et al. 2017). Moreover, severe HDP was defined as blood pressure ≥ 160/110 mmHg (Ohkuchi et al. 2017). GDM was diagnosed if at least one abnormal plasma glucose value (≥ 92, 180, and 153 mg/dl for fasting, one-hour, and two-hour plasma glucose concentrations, respectively) was noted after a 75-g oral glucose tolerance test (Wendland et al. 2012). Placental malposition was defined as placenta previa or a low-lying placenta. Fetal malpresentation was defined as any fetal presentation other than cephalic presentation. PPH was defined as active bleeding, including amniotic fluid exceeding 500 mL in a vaginal delivery or 1000 mL in a cesarean delivery within 24 hours of delivery (Minakami et al. 2014). SGA was defined as infants with a weight below the 10th percentile in each gestational week (Itabashi et al. 2010). Pregestational body mass index was calculated according to the World Health Organization standard (bodyweight [kg]/height [m^2]).

Statistical analysis

The Mann-Whitney U test was used to analyze continuous variables, such as maternal age, and the chi-square test (or Fisher's exact test when the expected frequency was < 5) was used to analyze categorical variables, such as the incidence of obstetric complications. We used Kaplan-Meier analysis and the log-rank test for examining the statistical differences in the gestational age at delivery between the case group (patients with adenomyosis) and control group A. Next, to analyze whether different types of adenomyosis affect the pregnancy complications, patients with adenomyosis were divided into two groups (focal adenomyosis group or diffuse adenomyosis group).

We used Kaplan-Meier analysis and the log-rank test to test for statistical differences in the gestational age at delivery between the diffuse and focal adenomyosis groups. Finally, the Mann-Whitney U test was used to analyze continuous variables, and the chi-square test (or Fisher's exact test when the expected frequency was < 5) was used to analyze categorical variables, such as maternal age and the incidence of obstetrical complications, between the diffuse adenomyosis group and control group B and between the focal adenomyosis group and control group C. The significance level was set at $P < 0.05$. All analyses were performed using Bell Curve for Excel (Social Survey Research Information Co., Ltd, Tokyo) and IBM SPSS Statistics 25 (IBM Corp., Armonk, NY).

Results

Effects of adenomyosis on pregnancy outcomes

In the first case-control study, the data for 61 women with adenomyosis and 244 women without adenomyosis (control group A) were extracted after matching for age, parity, and ART. Table 1 provides an overview of the baseline characteristics of the adenomyosis and control groups. Maternal age (35.2 ± 4.5 years vs. 35.2 ± 4.6 years, P = 0.91) and the rates of nulliparity (34.4% vs. 40.2%, P = 0.42) and ART (32.8% vs. 33.2%, P = 0.95) were similar in both groups. Other characteristics between the adenomyosis and control groups were similar, except for birth weight; the median gestational age at delivery was lower in the adenomyosis group (36.8 ± 3.9 weeks vs. 38.4 ± 2.0 weeks, P = 0.001; Table 2).

Kaplan-Meier analysis (Fig. 1) showed a significant difference in the gestational duration between the adenomyosis and control groups (log-rank test, P = 0.03). The incidence of obstetrical complications and perinatal outcomes are presented in Table 2. Preterm labor was noted for 13 of 61 (21.3%) women in the adenomyosis group and 23 of 244 (9.4%) women in the control group; thus, preterm labor was significantly more frequently noted in the adenomyosis group than in the control group (odds ratio [OR], 2.60; 95% confidence interval [CI], 1.23-5.50).

HDP developed in 8 of 61 (13.1%) women in the adenomyosis group and 13 of 244 (5.3%) women in the control group; thus, HDP was noted significantly more frequently in the adenomyosis group (OR, 2.68; 95% CI, 1.06-6.80). Moreover, the incidence of severe HDP was higher in the adenomyosis group (9.8%) than in the control group (3.6%); however, the difference was not statistically significant (OR, 2.84; 95% CI, 0.97-8.34). In the adenomyosis group, 23 of 50 (46.0%) women underwent cesarean delivery; this rate was significantly higher than that in the control group (42/201 women [20.9%]; OR, 3.22; 95% CI, 1.68-6.19).

PPH developed in 35 of 61 (57.3%) women in the adenomyosis group and 90 of 244 (36.8%) women in the control group; thus, PPH was significantly more frequently noted in the adenomyosis group (OR, 2.30; 95% CI, 1.30-4.07). Furthermore, the incidence of PPH was examined

Table 1. Baseline characteristics of the study population.

Variable	Adenomyosis group n = 61	Control group n = 244	*P* value
Maternal age, years	35.2 ± 4.5	35.2 ± 4.6	0.88
Nulliparity	21 (34.4)	98 (40.2)	0.42
IVF	20 (32.8)	81 (33.2)	0.95
Pre-pregnancy BMI, kg/m^2	21.3 ± 2.6	21.5 ± 3.3	0.82
Male sex	31 (50.8)	119 (48.8)	0.86
Birth weight, g	2,639 ± 706.5	2,947 ± 520.0	0.003

Values are presented as mean ± standard deviation or as number (%).
BMI, body mass index; IVF, *in vitro* fertilization.

Table 2. Comparison of the pregnancy outcomes between the adenomyosis group and control group A.

	Adenomyosis group n = 61	Control group A n = 244	*P* value	Odds ratio (95% CI)
Preterm labor	13 (21.3)	23 (9.4)	0.01	2.60 (1.23-5.50)
Gestational age at delivery	36.8 ± 3.9	38.4 ± 2.0	0.001	–
HDP	8 (13.1)	13 (5.3)	0.045	2.68 (1.06-6.80)
Severe HDP	6 (9.8)	9 (3.6)	0.09	2.84 (0.97-8.34)
GDM	9 (14.8)	21 (8.6)	0.15	1.83 (0.80-4.25)
pPROM	5 (8.2)	11 (4.5)	0.33	1.89 (0.63-5.66)
Placental malposition	5 (8.2)	8 (3.3)	0.14	2.63 (0.83-8.36)
Fetal malpresentation	5 (8.2)	8 (3.3)	0.14	2.63 (0.83-8.36)
Cesarean delivery†	23/50 (46.0)	42/201 (20.9)	< 0.001	3.22 (1.68-6.19)
PPH	35 (57.3)	90 (36.8)	0.004	2.30 (1.30-4.07)
PPH in cesarean delivery†	19/23 (82.6)	15/42 (35.7)	< 0.001	8.55 (2.45-29.8)
PPH in vaginal delivery	11/27 (40.7)	60/159 (37.7)	0.76	1.13 (0.49-2.61)
SGA infant	8 (13.1)	24 (9.8)	0.45	1.38 (0.59-3.25)
UA pH	7.31 ± 0.07	7.30 ± 0.06	0.50	–

Values are presented as number (%) or as mean ± standard deviation.
CI, confidence interval; HDP, hypertensive disorders of pregnancy; GDM, gestational diabetes mellitus; pPROM, preterm premature rupture of membranes; PPH, postpartum hemorrhage; SGA, small for gestational age; UA, umbilical artery.
†Cesarean delivery due to a previous cesarean delivery or previous uterine surgery were excluded.

separately for cesarean delivery and vaginal delivery. In cesarean delivery cases, PPH developed in 19 of 23 (82.6%) women in the adenomyosis group and 15 of 42 (35.7%) women in the control group; hence, PPH was significantly more frequently reported in the adenomyosis group (OR, 8.55; 95% CI, 2.45-29.8). Conversely, in cases of vaginal delivery, PPH developed in 11 of 27 (40.7%) women in the adenomyosis group and 60 of 159 (37.7%) women in the control group; there was no difference in the frequency in the adenomyosis group (OR, 1.13; 95% CI, 0.49-2.61).

Effects of diffuse or focal adenomyosis on pregnancy outcomes

Subsequently, the patients were categorized into the following two groups according to the type of adenomyosis: 41 women with diffuse adenomyosis and 20 women with focal adenomyosis. Table 3 presents the clinical characteristics of women with diffuse and focal adenomyosis. The characteristics of the diffuse and focal adenomyosis groups were similar, except for gestational age at delivery in the diffuse adenomyosis group. The median gestational age at delivery was smaller for women in the diffuse adenomyosis group than for those in the focal adenomyosis group (35.8 ± 4.3 vs. 38.7 ± 1.4 weeks, $P = 0.004$).

Kaplan-Meier analysis (Fig. 2) indicated a significant difference in the gestational duration between the diffuse and focal adenomyosis groups (log-rank test, $P = 0.01$). A second case–control analysis (diffuse vs. control B or focal vs. control C) was performed to determine whether different types of adenomyosis affect the pregnancy-related complications.

To examine the effects of diffuse adenomyosis on the pregnancy complications, the data for 41 women with diffuse adenomyosis and 164 controls (group B) were extracted after matching for age, parity, and ART. The maternal age (36.1 ± 3.8 vs. 35.9 ± 3.8, $P = 0.76$) and rates of nulliparity (31.7% vs. 32.9%, $P = 0.88$) and ART (36.6% vs. 35.3%, $P = 0.88$) were similar in both groups (data not

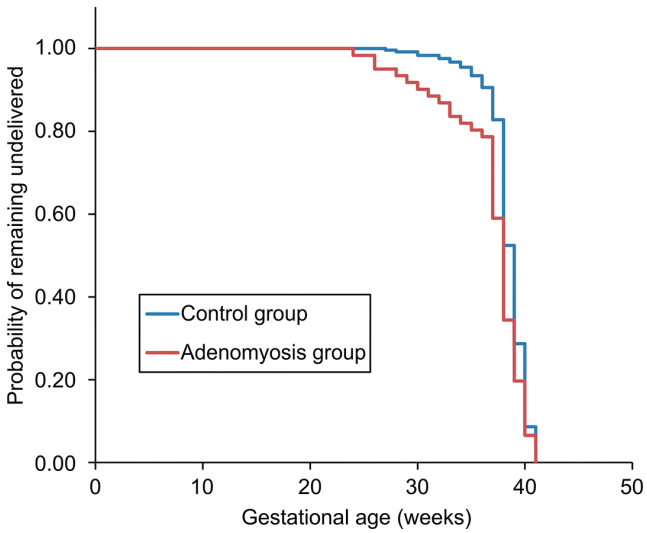

Fig. 1. Kaplan-Meier analysis of the gestational duration between the adenomyosis and control groups.
A significant difference in the gestational duration is noted between the adenomyosis (n = 61) and control A (n = 244) groups.

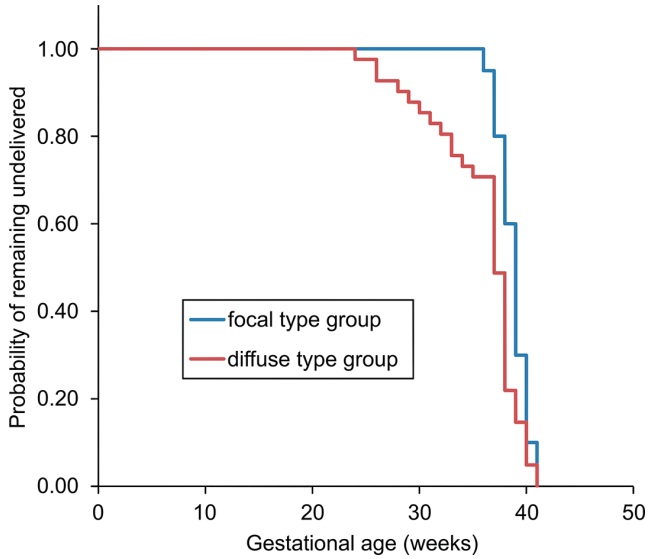

Fig. 2. Kaplan-Meier curve for the gestational age between the focal and diffuse adenomyosis groups.
A significant difference in the gestational duration is noted between the focal (n = 20) and diffuse adenomyosis (n = 41) groups.

shown). The other characteristics, except for birth weight (2499 ± 779.5 g vs. 2997 ± 487.3 g, $P < 0.001$), were similar between the diffuse adenomyosis group and control group B.

The diffuse adenomyosis group was significantly more likely to experience preterm labor (OR, 5.24; 95% CI, 2.15-12.8), HDP (OR, 3.54; 95% CI, 1.23-10.2), severe HDP (OR, 7.45; 95% CI, 1.70-32.6), pPROM (OR, 5.56; 95% CI, 1.42-21.7), cesarean delivery (non-reassuring fetal status, n = 5; placental malposition, n = 4; fetal malpresentation, n = 3; intrauterine infection, n = 1; maternal disorders, n = 1, labor arrest, n = 1, other causes, n = 4; OR, 6.76; 95% CI, 2.92-15.6), and PPH (OR, 3.01; 95% CI, 1.44-6.31) than the control group.

PPH development was examined for cesarean delivery and vaginal delivery separately. In cesarean delivery cases, PPH developed in 17 of 19 (89.5%) women in the diffuse adenomyosis group and 9 of 26 (34.6%) women in the control group; thus PPH was significantly more frequently noted in the adenomyosis group (OR, 16.1; 95% CI, 3.01-85.6). In the vaginal delivery cases, PPH developed in 7 of 12 (58.3%) women in the diffuse adenomyosis group and 51 of 111 (45.9%) women in the control group; however, the differences in frequency were not statistically significant in the adenomyosis group (OR, 1.64; 95% CI, 0.49-5.50; Table 4). Although the difference in the incidence of placental malposition was not statistically significant (OR, 3.43; 95% CI, 0.88-13.4), the incidence of placental malposition was also greater in the diffuse adenomyosis group than in the control group (Table 4).

Finally, to examine the effects of focal adenomyosis on the pregnancy complications, the data of 20 women with focal adenomyosis and 80 controls (group C) were extracted after matching for age, parity, and ART. The maternal age (33.6 ± 5.5 vs. 33.6 ± 5.6, $P = 1.00$) and rates of nulliparity (40.0% vs. 40.0%, $P = 1.00$) and ART (25.0% vs. 25.0%, P

Table 3. Baseline characteristics of the patients with diffuse and focal adenomyosis.

Variable	Patients with diffuse adenomyosis n = 41	Patients with focal adenomyosis n = 20	*P* value
Maternal age, years	36.1 ± 3.8	33.6 ± 5.3	0.10
Gestational age at delivery	35.8 ± 4.3	38.7 ± 1.4	0.004
Nulliparity	13 (31.7)	32 (40.0)	0.52
IVF	15 (36.6)	20 (25.0)	0.40
Pre-pregnancy BMI, kg/m^2	21.0 ± 2.0	24.3 ± 2.9	0.70
Male sex	24 (58.5)	38 (47.5)	0.06
Birth weight, g	2,499 ± 779.5	2,976 ± 507.8	0.06

Values are presented as mean ± standard deviation or as number (%).
BMI, body mass index; IVF, *in vitro* fertilization.

Table 4. Comparison of the pregnancy outcomes between the diffuse adenomyosis group and control group B.

	Diffuse adenomyosis group n = 41	Control group B n = 164	*P* value	Odds ratio (95% CI)
Preterm labor	12 (29.3)	12 (7.3)	< 0.001	5.24 (2.15-12.8)
HDP	7 (17.0)	9 (5.5)	0.02	3.54 (1.23-10.2)
Severe HDP	5 (12.2)	3 (1.8)	0.009	7.45 (1.70-32.6)
GDM	7 (17.0)	25 (15.2)	0.78	1.14 (0.46-2.87)
pPROM	5 (12.2)	4 (2.4)	0.02	5.56 (1.42-21.7)
Placental malposition	4 (9.8)	5 (3.0)	0.08	3.43 (0.88-13.4)
Fetal malpresentation	3 (7.3)	9 (5.5)	0.71	1.36 (0.35-5.27)
Cesarean delivery†	19/31 (61.3)	26/137 (18.9)	< 0.001	6.76 (2.92-15.6)
PPH	29 (70.7)	73 (44.5)	0.003	3.01 (1.44-6.31)
SGA infant	6 (14.6)	14 (8.5)	0.25	1.84 (0.66-5.12)
PPH in cesarean† delivery	17/19 (89.5)	9/26 (34.6)	< 0.001	16.1 (3.01-85.6)
PPH in vaginal delivery	7/12 (58.3)	51/111 (45.9)	0.54	1.64 (0.49-5.50)
UA pH	7.31 ± 0.07	7.30 ± 0.06	0.60	–

Values are presented as mean ± standard deviation or as number (%).
CI, confidence interval; HDP, hypertensive disorders of pregnancy; GDM, gestational diabetes mellitus; pPROM, preterm premature rupture of membranes; PPH, postpartum hemorrhage; SGA, small for gestational age; UA, umbilical artery.
†Cesarean deliveries due to a previous cesarean delivery or previous uterine surgery were excluded.

Table 5. Comparison of the pregnancy outcomes between the focal adenomyosis group and control group C.

	Focal adenomyosis group n = 20	Control group C n = 80	*P* value	Odds ratio (95% CI)
Preterm labor	1 (5.0)	7 (8.8)	1.00	0.55 (0.06-4.74)
HDP	1 (5.0)	2 (2.5)	0.49	2.05 (0.18-23.8)
Severe HDP	1 (5.0)	0 (0.0)	0.20	–
GDM	2 (10.0)	8 (10.0)	1.00	1.00 (0.20-5.12)
pPROM	0 (0.0)	1 (1.3)	1.00	–
Placental malposition	1 (5.0)	3 (3.8)	1.00	1.35 (0.13-13.7)
Fetal malpresentation	2 (10.0)	3 (3.8)	0.27	2.85 (0.44-18.3)
Cesarean delivery†	4/17 (23.5)	9/69 (13.0)	0.27	2.05 (0.55-7.69)
PPH	6 (30.0)	30 (37.5)	0.61	0.71 (0.25-2.06)
PPH in cesarean† delivery	2/4 (50.0)	4/9 (44.4)	1.00	1.25 (0.12-13.2)
PPH in vaginal delivery	4/13 (30.8)	23/60 (38.3)	0.76	0.71(0.20-2.59)
SGA infant	2 (10.0)	6 (7.5)	0.66	1.37 (0.26-7.36)
UA pH	7.31 ± 0.07	7.31 ± 0.06	0.65	–

Values are presented as mean ± standard deviation or as number (%).
CI, confidence interval; HDP, hypertensive disorders of pregnancy; GDM, gestational diabetes mellitus; pPROM, preterm premature rupture of membranes; PPH, postpartum hemorrhage; SGA, small for gestational age; UA, umbilical artery.
†Cesarean deliveries due to a previous cesarean delivery or previous uterine surgery were excluded.

= 1.00) were similar in both groups (data not shown). The incidence of obstetric complications and perinatal outcomes were not significantly different between the focal adenomyosis group and the control group (Table 5).

Discussion

The main results of this study are, as followed: first, women with adenomyosis were more likely to be associated with preterm labor, HDP, cesarean delivery, and PPH. Second, among women with uterine adenomyosis, diffuse adenomyosis was associated preterm labor, HDP, severe HDP, pPROM, cesarean delivery, and PPH. In contrast, focal adenomyosis may not be associated with poor pregnancy outcomes. To the best of our knowledge, this is the first study to clarify the association between adenomyosis, especially the diffuse type, and poor pregnancy outcomes in women in a multicenter setting.

An increase in the incidence of HDP in the adenomyosis group was an important finding. During pregnancy, invasion of the trophoblasts in the endometrium and myo-

metrial junctional zone induces decidualization and unique vascular changes. Impaired decidualization of the myometrial spiral arteries is a predisposing factor for failed intravascular trophoblast invasion (Brosens et al. 2010, 2013; Tamura et al. 2017). Defective deep placentation has been associated with HDP (Brosens et al. 2010, 2013; Tamura et al. 2017). Our result showing an increased risk of HDP in pregnant women with adenomyosis may be due to the detrimental effects of adenomyosis on this process. Although previous studies have clarified the association between HDP and SGA infants (Verlohren et al. 2012; Figueras and Gratacós 2014), our study showed no significant difference in the SGA infant rates between the adenomyosis and control groups. However, a type II error may have occurred because of the sample size.

Another important finding of our study was that cesarean delivery was significantly more common in the adenomyosis group than in the control group. Several studies have reported that the possibility of cesarean delivery increases in women with adenomyosis (Mochimaru et al. 2015; Hashimoto et al. 2018). The following reasons may be considered. First, placental malposition was more frequently observed in women with adenomyosis than in those without. A plausible mechanism is that the adenomyosis lesion in the uterine body has a detrimental effect on the normal implantation process and disturbs the implantation site, resulting in the development of placental malposition (Hashimoto et al. 2018).

Second, several studies have reported that pregnant women with adenomyosis had higher rates of pPROM than those without (Juang et al. 2007; Mochimaru et al. 2015). Prostaglandin has been implicated as a risk factor for pPROM as it causes uterine irritability and collagen degradation within the fetal membranes (Tjugum and Norström 1985; Juang et al. 2007). Previous studies have reported an increased level of prostaglandin in women with adenomyosis (Koike et al. 1994; Juang et al. 2007). Although the underlying pathophysiological pathways should be investigated, prostaglandin may play a role in the association between adenomyosis and pPROM. As the number of cases of intrauterine infection and fetal distress owing to pPROM have increased, the frequency of cesarean deliveries in the preterm period increased.

Third, cesarean delivery as the indication of fetal malpresentation was more common in women with adenomyosis than in those without. This is because adenomyosis narrows the intrauterine cavity and decreases the uterine extensibility, like a uterine myoma (Mochimaru et al. 2015). We found no significant differences with respect to the placental malposition, pPROM, and fetal malpresentation between the adenomyosis and control groups. However, as with HDP, a type II error may have occurred because of the sample size. Women in the adenomyosis group tended to have higher complication rates than those in the control groups; however, the difference was not significant. Owing to this tendency, we concluded that cesarean delivery was more common in the adenomyosis group than in the control group.

Another important finding was the increased incidence of PPH in the adenomyosis group. The presence of adenomyosis could have impaired the functionality of the gravid uterus, thereby, increasing uterine atony and leading to PPH development (Vlahos et al. 2017). In addition, the high frequency of HDP, which is a risk factor for PPH (von Schmidt auf Altenstadt et al. 2013; Minakami et al. 2014), in the adenomyosis group may be responsible for this result. In particular, the amount of blood loss during cesarean delivery was significantly higher in the adenomyosis group than in the control group (1203 ± 493 mL vs. 936 ± 509 mL, P = 0.008; data not shown). Therefore, it may be important to prepare for autologous blood transfusion in the late third trimester for women with adenomyosis, and at the time of cesarean section, it may be effective to consider using Bakri balloon tamponade since the Bakri device is more effective in managing postpartum hemorrhage, if inserted early after delivery (Vintejoux et al. 2015).

To date, previous studies have not evaluated whether the type of adenomyosis affects the pregnancy complications. According to previous reports, diffuse adenomyosis is more common than the focal type. In a study, the prevalence of diffuse and focal types of adenomyosis was 81.7% and 18.3%, respectively (Sofic et al. 2016). In another study, the prevalence was 66.7% and 33.3%, respectively (Byun et al. 1999). In the present study, 65.6% (40/61) of pregnancies involved diffuse adenomyosis. Previous studies claimed that adenomyosis is associated with poor pregnancy outcomes (Juang et al. 2007; Mochimaru et al. 2015; Tamura et al. 2017; Hashimoto et al. 2018). Here, we demonstrated that uterine adenomyosis, especially the diffuse type, was associated with high-risk perinatal cases.

Considering the increased incidence of HDP, pPROM, placental malposition, fetal malpresentation, and PPH, women with diffuse adenomyosis, which is marked by widespread lesions compared to the focal type, may be prone to developing pregnancy complications. We believe that this study provides obstetricians with useful information for improving prenatal management and counseling for patients with adenomyosis in the clinical setting.

There are certain limitations of this study. First, it may be difficult to extrapolate our results to the general population because of the relatively small sample size. Therefore, a large-scale multicenter prospective cohort study is required to confirm these results in the general population. Second, the data on gestational weight gain, intake of alcohol and caffeine, antiphospholipid, thyroid disease, family history, and socioeconomic status, which may affect the pregnancy complications, were not considered in this study (Harita et al. 2012; Räisänen et al. 2013; Minakami et al. 2014). The women in the present study may have been affected by the aforementioned risk factors.

Although some limitations exist, the strength of this study is the selection of case and control groups from mul-

tiple institutions to reduce the effect of selection bias. This is the first study to examine the causality between adenomyosis and pregnancy in a multicenter case-control study.

In conclusion, although studies with a larger sample size are required, it appears that adenomyosis, especially the diffuse type, is significantly associated with perinatal adverse outcomes. Our findings provide valuable evidence that women with diffuse adenomyosis require more careful perinatal management than previously thought.

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Conflict of Interest

The authors declare no conflict of interest.

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