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Original Article

Uterine wall thickness at the second trimester can predict subsequent preterm delivery in pregnancies with adenomyosis

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ABSTRACT

Objectives: We assessed the usefulness of ultrasonography (USG) findings of adenomyosis during pregnancy in the prediction of subsequent preterm delivery.**Materials and methods:** We included consecutive pregnant women who underwent first trimester ultrasonography in our institution, confirmed as having adenomyosis and subsequently delivered in our institution from January 2006 to April 2018. The subjects were classified into two groups: preterm delivery group and term delivery group. Information of maximal uterine wall thickness measured at first trimester and second trimester, maternal characteristics, pregnancy outcomes, and neonatal outcomes were reviewed and compared between preterm and term delivery group.**Results:** A total of 57 pregnancies were included in this study, and 14 women (24.5%) delivered before 37 weeks of pregnancy. The women from the preterm delivery group had a significantly thicker uterine wall during the second trimester compared to the women from the term delivery group (4.49 ± 1.62 cm vs. 3.05 ± 1.6 cm, $p = 0.004$). From the first trimester to the second trimester of pregnancy, uterine wall thickness showed a significantly smaller decrease in the preterm delivery group than the term delivery group (-0.42 ± 0.93 cm vs. -1.04 ± 0.89 cm, $p = 0.02$). By receiver operating characteristics (ROC) curve analysis, uterine wall thickness greater than 4.6 cm in the second trimester of pregnancy showed 57.1% sensitivity, 86.1% specificity, 57.1% positive predictive value (PPV) and 86.1% negative predictive value (NPV) for subsequent preterm delivery (area under curve = 0.758).**Conclusions:** Uterine wall thickness measurement in second trimester can help to identify preterm delivery in pregnant women with adenomyosis.© 2019 Taiwan Association of Obstetrics & Gynecology. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Adenomyosis is defined as a condition in which the uterine endometrial glands and stroma are present within the uterine myometrium. Traditionally, the definitive diagnosis of adenomyosis was made through histological examination after hysterectomy. Depending on various diagnostic methods, reports on the incidence of adenomyosis have ranged from 5% to 70% [1]. Imaging methods such as ultrasonography (USG) and magnetic resonance imaging (MRI) are highly accurate diagnostic tools for adenomyosis [1–4]. Transvaginal ultrasonography (USG) and MRI have shown similar accuracy in the

diagnosis of adenomyosis [5]. For pregnant women, USG is a safer and more convenient tool than MRI for diagnosis of adenomyosis; therefore, USG is commonly used for initial study [5–7].

Pregnancies complicated by adenomyosis are associated with several adverse pregnancy outcomes, such as subfertility, higher preterm delivery rate, more frequent fetal growth restriction (FGR), fetal malpresentation, preeclampsia (PE), and postpartum hemorrhage (PPH) [4,8–10]. An inflammatory process observed in adenomyosis has been implicated as a biochemical mechanism in preterm labor, preterm premature rupture of membranes (PPROM), and preterm delivery in pregnancies with adenomyosis. Higher prostaglandin (PG) level was found in adenomyosis tissue and the peritoneal fluid of women with endometriosis or adenomyosis [11–13]. PG contributes to uterine irritability and induction of uterine contractions causing preterm labor [14]. PG may also regulate the tensile properties of the fetal membranes by

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influencing collagen synthesis [15], resulting in weakness and rupture of membranes.

As maternal age at the first childbearing gets older than ever before, and pregnancies complicated by adenomyosis are commonly encountered in prenatal check nowadays [8,16]. Korean statistics showed that the average age at which women give first birth and the rate of pregnant women over 35 have increased for years (from 30.6 in 2007 to 32.2 years in 2015, from 18.7% in 2012 to 29.3% in 2017, respectively) [17].

With this background, we found few studies evaluating the association between adenomyosis and preterm delivery [4,9], and to the best of our knowledge, no study has investigated the predictive factors for preterm delivery based on USG findings during pregnancy in patients with adenomyosis. In this study, we aimed to find the USG findings of adenomyosis (location and maximal uterine wall thickness) that are associated with increase in subsequent preterm delivery.

Methods

This is a retrospective study of pregnant women diagnosed as adenomyosis before pregnancy and/or in the first trimester of pregnancy by USG in our institution from January 2006 to April 2018. Women with pregnancy complicated by pre-existing medical illnesses, multiple pregnancy, alleged uterine anomaly, chorioamnionitis and/or uterine myoma were excluded. Diagnosis of chorioamnionitis was based on Gibbs criteria. Adenomyosis was diagnosed on the basis of following USG criteria [2,5,18,19] and reviewed by a single researcher. Because the uterine wall thickness changed when there was contraction of the uterus [20], we did not measure the uterine wall when the patients have uterine contractions.

We examined adenomyosis at 6–12 weeks of gestation in the first trimester and at 16–21 weeks of gestation in the second trimester. Our USG criteria for diagnosis of adenomyosis included two or more of the following: (1) thickening and asymmetry of the anterior and posterior myometrial walls, (2) increased echotexture of the myometrium, and (3) heterogeneous, indistinctly marginated areas in the myometrium (Fig. 1). Focal lesions less than 2 cm in diameter were excluded to secure diagnostic reliability. We examined the characteristics of adenomyosis, such as location (anterior, posterior, both) and maximal thickness of the uterine wall checked during the first and second trimester of pregnancy. The maximal vertical uterine wall thickness included the whole

myometrium and the adenomyosis lesion, and it was measured on the anterior or posterior wall of the uterus by several examiners, but reviewed by one examiner. Fig. 1 represents the measurement of maximal uterine wall thickness by USG. We also collected the value of cervical length measured by transvaginal USG at 16–22 weeks of gestation. All women in this study were regularly followed after delivery until completion of the medical record review.

We reviewed the baseline maternal characteristics of maternal age, body mass index, parity, previous preterm delivery history, and pregnancies achieved by assisted-reproductive technology. We collected pregnancy outcomes of gestational age at delivery, mode of delivery, fetal malpresentation, preterm delivery, PE, small for gestational age (SGA), FGR, and PPH. Fetal malpresentation was defined as any fetal presentation other than cephalic. We classified SGA neonates as having less than 10th percentile for their gestational age [21]. FGR was defined as a fetus whose estimated weight was below the 10th percentile with a pathologic response on umbilical or middle cerebral artery (MCA) Doppler USG. PPH was defined as an estimated blood loss of 1000 mL or more for a vaginal delivery and 1500 mL or more for a cesarean delivery [22]. Neonatal outcomes of birth weight, 1-minute Apgar score, 5-minute Apgar score, admission to the neonatal intensive care unit (NICU) and fetal major anomaly were also examined.

The data from continuous variables were compared by the paired *t*-test, *t*-test, and Wilcoxon rank sum test as appropriate. Categorical variables were compared by the chi-square test and Fisher's exact test. Multiple logistic regression analysis was performed to evaluate the potential confounding factor effecting preterm birth. ROC curve analysis was performed to determine the diagnostic value of uterine wall thickness for preterm delivery. Comparison of area under the curve (AUC) was performed by a non-parametric approach of DeLong for two correlated AUCs. Optimal cut-off values were defined based on their highest diagnostic accuracy in the ROC curves. Sensitivity, specificity, PPV, and NPV were also calculated to assess the diagnostic utility of each parameter in predicting preterm delivery. A power analysis for equality test was conducted due to small case number. Analysis was completed with SAS version 9.4 (SAS Institute, Cary, NC, USA), and the level of significance was defined as $p < 0.05$. The study was approved by the Institutional Review Board (IRB No. 2018-01-138).

Results

As shown in Table 1, among the 57 pregnant women in this study, 24.5% delivered preterm before 37 weeks of pregnancy. The

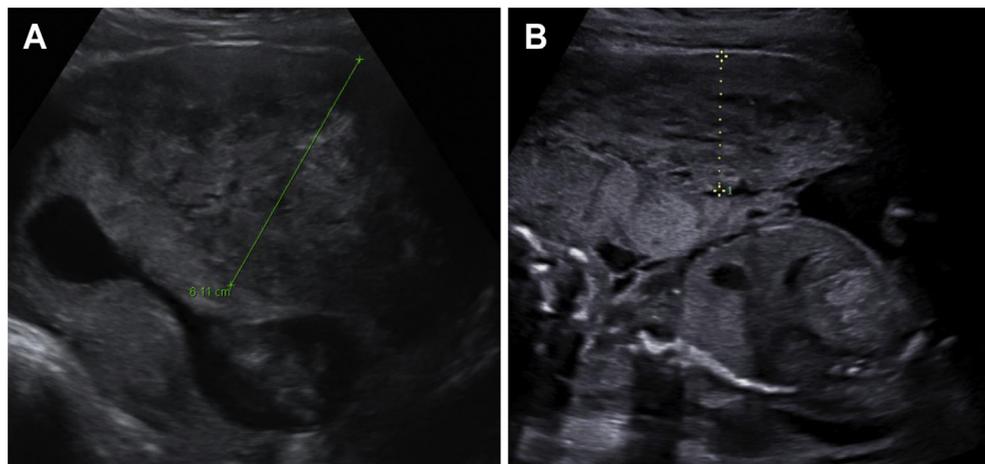


Fig. 1. Measurement of uterine wall thickness by transabdominal ultrasonography in the first trimester (A) and the second trimester (B) of pregnancy. The maximal vertical thickness of the anterior or posterior uterine wall affected by adenomyosis was measured.

rate of assisted reproductive technology (ART) was 15.7% in this population. Of note, incidence of preeclampsia and FGR was 15.7% and 19.2%, respectively, which was higher than the general incidence of 2–5% of preeclampsia and 10% of FGR [23,24].

Table 1 summarizes the comparisons of the maternal characteristics and pregnancy and neonatal outcomes between the preterm delivery group and the term delivery group. The mean gestational age at delivery was 33.4 ± 2.79 weeks and 38.9 ± 1.15 weeks of gestations in the preterm delivery group and term delivery group, respectively. The rates of PE and NICU admission were higher and birth weight was lower in the preterm delivery group than in the term delivery group. Comparisons of the other pregnancy and neonatal outcomes showed no significant differences between the two groups.

Follow-up after delivery revealed that no one underwent hysterectomy, 51 women used painkillers, 2 women used hormone-releasing intrauterine devices, and 2 women used oral contraceptives for severe dysmenorrhea.

To analyze the relationship of USG findings and subsequent preterm delivery, we compared maximal uterine wall thickness and location of adenomyosis between the preterm delivery group and the term delivery group (Table 2). The locations of the adenomyosis lesions were mostly on one side of the uterus (rather than on both sides) in both groups. In the first trimester, the median gestational age at USG performed was not different between two groups (10.1 week vs. 9.1 week, $p = 0.76$) and uterine wall thickness, including adenomyosis lesions, was not significantly different between the preterm and the term delivery groups (4.91 ± 1.83 cm vs. 4.09 ± 1.55 cm, $p = 0.09$). In the second trimester, the median gestational age at measurement was 21.2 week and 21.0 week, which showed no difference. However, uterine wall thickness was significantly thicker in the preterm delivery group compared to term delivery group (4.49 ± 1.62 cm vs. 3.05 ± 1.6 cm, $p = 0.004$). The cervical length measurement was available in 51 out of 57 patients in the second trimester of pregnancy. There was no significant difference in cervical length between two groups (3.42 ± 0.95 vs. 3.73 ± 0.67 p = 0.210). As not shown in Table 2, short cervical length less than 2.5 cm was more frequently found in the preterm group than in the term group, but this difference did not reach statistical significance (15.38% vs. 2.63%, $p = 0.156$). On multivariable logistic regression analysis, maximal uterine wall thickness at 2nd trimester (OR: 3.177, 95% CI: 1.219–8.283) was significant predictors of preterm delivery (see Table 3).

When we analyzed the differences in uterine wall thickness measured in the first and the second trimester of pregnancy, the uterine wall thickness showed a decreasing trend. The changes in uterine wall thickness from the first to second trimester of pregnancy are presented as a line plot (Fig. 2). The decrease in uterine wall thickness was significantly greater in the term group compared to the preterm group (-1.04 ± 0.89 cm vs. -0.42 ± 0.93 cm, $p = 0.02$).

In the ROC curve analysis for prediction of preterm delivery, uterine wall thickness in the first trimester of pregnancy showed an AUC of 0.650 (0.470–0.830) (Fig. 3A) and presented a diagnostic performance of 78.5% sensitivity, 62.7% specificity, 40.7% PPV, and 90.0% NPV at a diagnostic threshold of 3.9 cm. In the second trimester, uterine wall thickness showed an AUC of 0.758 (0.612–0.903) for prediction of preterm birth less than 37 weeks of gestation (Fig. 3B). With the cutoff value of above 4.6 cm in uterine wall thickness, the sensitivity, specificity, PPV, and NPV were 57.1%, 86.1%, 57.1%, and 86.1%, respectively. When we compared diagnostic performance of uterine wall thickness in the first trimester and second trimester, uterine wall thickness in the second trimester of pregnancy showed significantly greater AUC value for prediction of subsequent preterm delivery (non-parametric approach of DeLong, $p = 0.007$).

We evaluated the effect of confounding variables (maternal age, BMI, multiparity, ART, prior preterm birth history, preeclampsia, uterine wall thickness at 1st trimester and 2nd trimester) related to preterm delivery by multivariable logistic regression analysis. As a result, pregnant women with thicker uterine wall at second trimester had a significantly higher incidence of preterm delivery (adjusted odds ratio of 3.177 with 95% confidence interval of 1.219–8.283). However, uterine wall thickness at first trimester was not associated with increased the preterm birth in multivariable analysis.

We compared the baseline characteristics and pregnancy outcome of the study population according to the cutoff value of uterine wall thickness determined by ROC analysis stated above. As not shown in Table, patients with adenomyosis with uterine wall thickness above 4.6 cm showed significant higher rate of preterm delivery (57.1% vs. 14.0%, $p = 0.001$) and ART (50.0% vs. 4.7%, $p < 0.05$).

In power analysis of equality test, we assumed the event rate of 15% for preterm birth in the reference group (i.e. uterine wall thickness at 2nd trimester <4.6 cm). With sample size of 57 and 14 of preterm delivery group, the expected power was 19.7% and 73.0% to ensure significant 2.5% and 5.9% increment in event rate

Table 1
Maternal characteristics, pregnancy and neonatal outcomes between the preterm delivery group and the term delivery group.

	Preterm delivery (n = 14)	Term delivery (n = 43)	p-value
Maternal age (years)	35.7 ± 2.7	35.3 ± 3.6	0.726
Body mass index (kg/cm ²)	21.0 ± 1.6	22.0 ± 2.9	0.121
Multiparity	6 (42.9)	23 (53.5)	0.490
Assisted reproductive technology	3 (21.4)	6 (14.0)	0.674
Prior preterm birth	2 (14.3)	4 (9.3)	0.629
Preeclampsia	5 (35.7)	4 (9.3)	0.032
FGR	4 (28.6)	7 (16.3)	0.436
Gestational age at delivery (weeks)	33.4 ± 2.8	38.9 ± 1.2	<0.001
Fetal malpresentation	2 (14.3)	3 (7.0)	0.587
Cesarean delivery	7 (50.0)	20 (46.5)	0.820
Postpartum hemorrhage	0	1 (2.3)	1.000
Live birth	14 (100)	43 (100)	1.000
Birth weight (g)	1995.4 ± 564.1	3087.2 ± 487.5	<0.001
Male	10 (71.4)	24 (55.8)	0.301
SGA	3 (21.4)	7 (16.3)	0.694
Apgar score at 1 min < 4	0	1 (2.3)	1.000
Apgar score at 5 min < 7	0	0	
NICU admission	7 (50.0)	1 (2.3)	<0.001
Fetal anomaly	0	1 (2.3)	1.000

Data are presented as mean \pm standard deviation or number (%).

FGR, fetal growth restriction; SGA, small for gestational age; NICU, neonatal intensive care unit.

Table 2
Ultrasonographic findings of adenomyosis in the preterm delivery group and the term delivery group.

	Preterm delivery (n = 14)	Term delivery (n = 43)	p-value
Location of adenomyosis			0.629
Anterior or posterior uterine wall	12 (85.7)	39 (90.7)	
Both	2 (14.3)	4 (9.3)	
Maximal uterine wall thickness at 1st trimester (cm)	4.91 ± 1.83	4.09 ± 1.55	0.097
Gestational age at exam (week)	10.1 (6.0, 13.1)	9.1 (7.1, 13.6)	0.767
Maximal uterine wall thickness at 2nd trimester (cm)	4.49 ± 1.62	3.05 ± 1.60	0.004
Gestational age at exam (week)	21.2 (20.1, 23.0)	21.0 (16.5, 21.8)	0.056
Cervical length (cm) ^a	3.42 ± 0.95	3.73 ± 0.67	0.210
Amniotic fluid index (cm)	16.1 ± 3.79	16.5 ± 2.82	0.666

Data are presented as mean ± standard deviation/median (minimum–maximum)/number (%).

^a Data from 6 cases were not available.

(corresponding OR = 1.2 and 1.5) for the thicker group, respectively. With this sample size and preterm delivery group, the minimum increment of 6.6% in preterm delivery rate (corresponding OR = 1.56) for the thicker group can be detected with the 80% power. Note that significance level of 5% was considered [25].

Discussion

Our data showed that adenomyosis thickness measured at second trimester can be useful to identify the subsequent preterm delivery less 37 weeks of gestation. In detail, uterine wall thickness greater than 4.6 cm at second trimester showed 57.1% sensitivity and 86.2% specificity for subsequent preterm delivery.

We also demonstrated that the uterine wall thickness decreased significantly from the first trimester to the second trimester of pregnancy in all pregnancies with adenomyosis. However, the uterine wall thickness decreased significantly less in the preterm delivery group compared to the term delivery group.

Previous studies showed an association between adenomyosis and adverse pregnancy outcomes [4,9,10,26,27]. In particular, preterm delivery seems to be the most consistently observed adverse pregnancy outcome in pregnant women with adenomyosis. Women with adenomyosis showed a higher rate of preterm delivery than women without adenomyosis (24.4% vs. 9.3%, OR: 3.1, 95% CI: 1.2–7.2) [9]. In our study population, 24.5% of the women with adenomyosis had a preterm delivery. In this respect, our study yielded a consistent finding with previous studies that adenomyosis is significantly associated with preterm delivery.

The pathophysiology of preterm delivery in pregnancies with adenomyosis is uncertain and complicated. Uterine contractions caused by PG from adenomyosis tissue may contribute to preterm delivery. Moreover, myometrial stiffness might be altered in adenomyosis by the changes in myometrial structure. Adenomyosis

foci grow within the interfascial compartment of connective tissue between the fascicles of hypertrophic smooth muscle cells, and the lesions accompany myometrial hyperemia, lymphostasis, edema of perivascular myometrium tissue, and leiomyomatosis of myometrial perifocal hyperplasia [28–30]. These biochemical and pathologic changes would cause the aforementioned strong association between adenomyosis and preterm delivery. Our data showed that the uterine wall was thicker and less stretched during the second trimester of pregnancy in the preterm delivery group compared to the term delivery group. These results suggest the positive correlation of uterine wall thickness, myometrial stiffness, and PG production. We speculate that the uterine wall (even in severe adenomyosis) expands through secretory differentiation and/or possible regression of adenomyosis from the first trimester to the second trimester of pregnancy to provide quiescent space for

Table 3
Multiple logistic regression analyses of preterm delivery controlling for potential confounding variables.

	OR [95%CI]	p-value
Maternal age	1.102 [0.844–1.439]	0.629
Body mass index	0.794 [0.564–1.116]	0.183
Multiparity	0.883 [0.153–5.115]	0.889
Assisted reproductive technology	0.540 [0.059–4.925]	0.584
Prior preterm birth	2.399 [0.228–25.229]	0.466
Preeclampsia	5.794 [0.918–36.556]	0.061
Maximal uterine wall thickness at 1st trimester (cm)	0.521 [0.206–1.322]	0.170
Maximal uterine wall thickness at 2nd trimester (cm)	3.177 [1.219–8.283]	0.018

OR, odds ratio; CI, confidence interval.

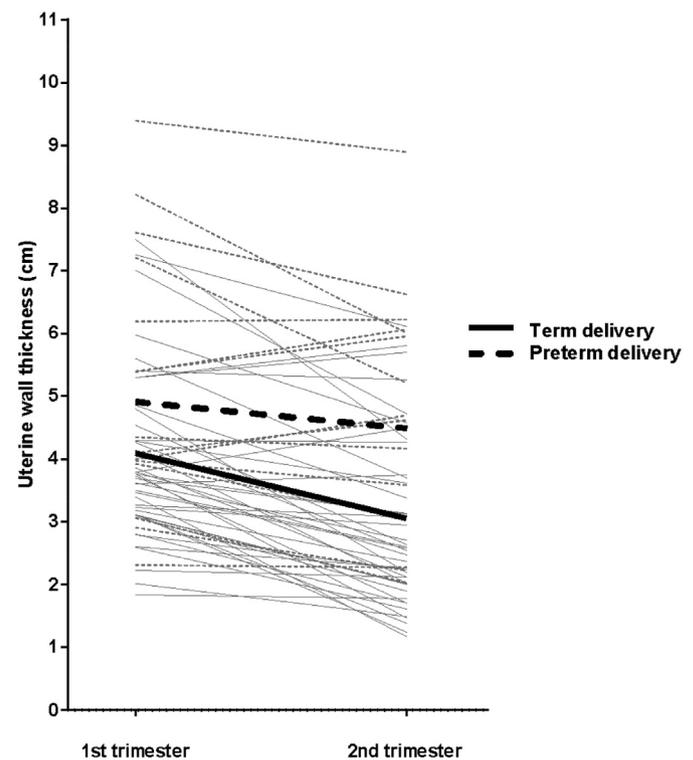


Fig. 2. Comparison of the changes in uterine wall thickness between the preterm delivery group and the term delivery group from the first trimester to the second trimester of pregnancy. Term delivery group (dashed line) showed significantly greater decrease in uterine wall thickness than the preterm delivery group (dotted line). Bold lines represent changes of average uterine wall thicknesses in the preterm and the term delivery group.

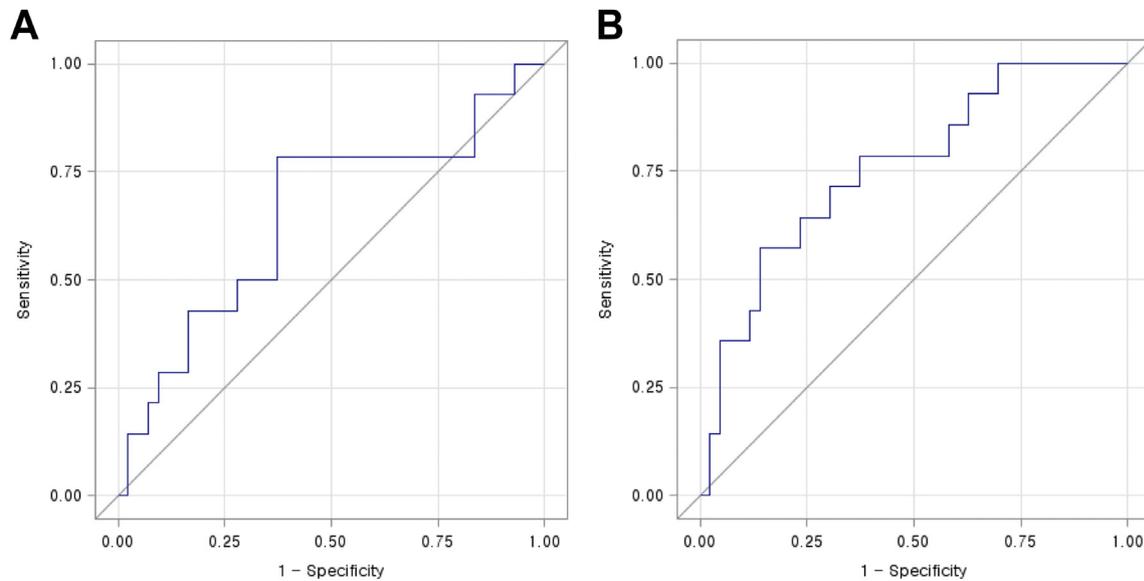


Fig. 3. The diagnostic thresholds of maximal uterine wall thickness provided by ROC curve analysis for prediction of preterm delivery. (A) Maximal uterine thickness in the first trimester of pregnancy (Cut-off value: 3.9 cm, AUC = 0.650) (B) Maximal uterine thickness in the second trimester of pregnancy (Cut-off value: 4.6 cm, AUC = 0.758).

the growing fetus. In this regard, vaginal progesterone treatment might have a role in preventing preterm delivery by influencing histologic changes in adenomyosis tissue during pregnancy.

The incidence of preeclampsia in the general population was reported to be 2–8% [31]. Failed remodeling of the spiral artery in the early stage and abnormal placentation leading to subsequent disruption of the syncytial architecture in the second stage are the main pathological process of preeclampsia [32]. In adenomyosis, the increased PG production and changes of the myometrial junctional zone could restrict remodeling of the myometrial spiral artery [29]. Eventually, abnormal placentation results in both FGR and preeclampsia. In our study, approximately 16% of pregnant women with adenomyosis developed PE, which was a higher rate than in the general population. Moreover, compared with the term delivery group, the preterm delivery group had a higher rate (9% vs. 36%) of PE in this study. These results suggest that thicker uterine walls produce a greater amount of PG production, leading to preterm birth. Therefore, pregnant women with adenomyosis should be counseled about the use of low dose aspirin for prevention of PE.

The definitive diagnosis of adenomyosis is confirmed through pathologic exams after hysterectomy. However, we could not compare the imaging findings with histopathologic findings because no patient in this study underwent hysterectomy. Considering that the average age at the time of delivery was 35 years, we presumed that patients wanted to preserve their fertility.

The limitations of our study are small sample size and measurement bias. As this study was retrospective, USG was not performed by one examiner; potential inter-observer bias could not be avoided. In regard to the diagnostic tool used in this study, USG is a common modality in clinical evaluation during pregnancy worldwide, although MRI provides a 3-dimensional measurement and is superior to USG in sensitivity and specificity [2].

Adenomyosis and preterm labor have similar biochemical pathways of uterine contraction; therefore, women with adenomyosis are at-risk for preterm delivery. Pregnant women who have adenomyosis should be counseled about potential complications, including preterm delivery and PE. In this regard, we believe that our findings will be useful for counseling and planning management in pregnant women with adenomyosis.

Conflict of interest

The authors report no conflict of interest.

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