







# The Risk of Preterm Births Among Pregnant Women With Adenomyosis

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**Objectives**—Few studies have examined the effect of adenomyosis on pregnancy outcomes. We aimed to evaluate the risk of preterm birth and low birth weight in women with adenomyosis diagnosed during pregnancy.

**Methods**—A computerized ultrasonography database was used to identify singleton pregnant women with adenomyosis in the first trimester from January 2010 to December 2011. Only cases with a known pregnancy outcome were included. We reviewed the medical records and analyzed pregnancy outcomes according to the presence of adenomyosis and conception method.

**Results**—Among 11,173 singleton pregnant women, adenomyosis was detected in 88 (0.8%), and 8316 pregnant women (including 72 with adenomyosis) were included. The adenomyosis group was associated with significantly higher rates of preterm birth and low birth weight than the non-adenomyosis group (12.5% versus 4.1%;  $P < .001$ ; 13.9% versus 3.1%;  $P < .001$ , respectively). In a subgroup analysis according to the conception method, incidences of preterm birth and low birth weight were not different in the non-adenomyosis group. However, the risks of preterm birth and low birth weight in the adenomyosis group were significantly higher in pregnant women who conceived by assisted reproductive technologies than in women who conceived naturally (28.0% versus 4.3%;  $P < .01$ ; 28.0% versus 6.4%;  $P < .05$ , respectively).

**Conclusions**—Ultrasonographic findings suggesting adenomyosis in early pregnancy were associated with increased risks of preterm delivery and low birth weight in women who conceived with the use of assisted reproductive technologies but not in women who conceived spontaneously.

**Key Words**—adenomyosis; assisted reproductive technologies; gynecology; low birth weight; obstetrics; premature birth; ultrasonography

Received December 13, 2016, from the Department of Obstetrics and Gynecology, Hankook General Hospital, Jeju, Korea (Y.J.S.); and Department of Obstetrics and Gynecology, Cheil General Hospital and Women's Healthcare Center, Dankook University College of Medicine, Seoul, Korea (D.W.K., J.H.C., M.Y.K., S.W.L., Y.J.H.). Manuscript accepted for publication October 27, 2017.

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## Abbreviations

ART, assisted reproductive technologies; CI, confidence interval; OR, odds ratio; US, ultrasonography

doi:10.1002/jum.14540

Adenomyosis is a pathologic condition that is characterized by the presence of ectopic endometrial glands and stroma within the myometrium<sup>1</sup> and can lead to menorrhagia, dysmenorrhea, dyspareunia, and subfertility.<sup>2</sup> The prevalence of adenomyosis ranges from 5% to 70%,<sup>2-5</sup> depending on the criteria. A definite diagnosis of adenomyosis is based on histopathologic findings, and it is mostly diagnosed in parous women in their 40s and 50s. However, asymptomatic adenomyosis may be incidentally diagnosed in women with gynecologic disease such as leiomyoma or cervical intraepithelial neoplasia. It is not easy to diagnose adenomyosis in asymptomatic young nulliparous women; however, with recently improved imaging techniques and the tendency to delay pregnancy, the frequency of pregnancy-associated adenomyosis has been increasing among pregnant women of advanced age and pregnancies achieved by assisted

reproductive technologies (ART).<sup>6,7</sup> Previous studies of pregnancy outcomes in pregnant women with adenomyosis are scarce because only histologic diagnoses of adenomyosis were possible in the past. Recently, Salim et al<sup>8</sup> reported that infertile women undergoing their first in vitro fertilization who had adenomyosis on ultrasonography (US) had lower clinical and ongoing pregnancy rates than women with a morphologically normal uterus (22.2% versus 47.2% and 11.1% versus 45.9%, respectively). However, a relationship between adenomyosis and subfertility is still controversial; some researchers believe that adenomyosis is not common in subfertile women, whereas others think that it plays a critical role in subfertility.<sup>9</sup>

To date, there are only 2 case-control studies of adenomyosis regarding pregnancy outcomes including preterm births.<sup>10,11</sup> Juang et al<sup>10</sup> reported that preterm delivery and preterm premature rupture of membranes were more common in pregnant women with adenomyosis. One more recent case-control study compared pregnancy outcomes between cases with adenomyosis and a normal uterus and concluded that adenomyosis was associated with an increased incidence of preterm delivery (41.7% versus 12.5%), premature rupture of membranes (19.4% versus 4.2%), and poor pregnancy outcomes compared with a control group.<sup>11</sup> However, these studies included small populations, and Juang et al<sup>10</sup> only assessed the incidence of adenomyosis among the population with preterm delivery or preterm premature rupture of membranes. There are few data on pregnancy outcomes because most cases of adenomyosis are diagnosed by hysterectomy in women older than 40 years, and it is difficult to diagnose asymptomatic adenomyosis during pregnancy. This study aimed to assess the prevalence of preterm birth and low birth weight in pregnant women with adenomyosis and to investigate whether these outcomes are different according to the method of conception.

## Materials and Methods

We retrospectively reviewed the medical records and US database of singleton pregnant women with a diagnosis of adenomyosis by US in the first trimester of pregnancy from January 2010 to December 2011. Among them, only cases with known pregnancy outcomes that delivered at later than 20 gestational weeks were included in this study. Ultrasonographic examinations were performed with a Voluson E8 US device (GE Healthcare,

Zipf, Austria) and an EnVisor HD device (Philips Healthcare, Bothell, WA). The US data were obtained and analyzed in both grayscale and color Doppler modes. The diagnosis of adenomyosis was based on the US findings during early gestation according to the presence of 2 or more of the following criteria from previous studies<sup>12–14</sup>: (1) a globular or asymmetric uterus unrelated to the presence of fibroids, (2) a poorly defined heterogeneous myometrium, (3) a distorted and heterogeneous myometrial echo texture, (4) irregular myometrial cystic lesions, (5) hypoechoic linear striations, and (6) an irregular endometrial-myometrial junction. All cases showed the presence of criterion 1 along with criterion 2 or criterion 3 among our inclusion criteria as US features of the adenomyosis. The characteristics of the study population that were collected were maternal age at delivery, parity, abortion history, method of conception, and delivery mode. We routinely perform transvaginal US between 7 and 9 weeks to verify the gestational week, record the presence of multiple pregnancies, and evaluate the uterus and adnexa. We document the presence of adenomyosis at that time. The patients were divided into adenomyosis and non-adenomyosis groups, according to the presence of US findings of adenomyosis during early pregnancy, and the outcomes of the pregnancies with adenomyosis were compared with those of the women who did not have a diagnosis of adenomyosis. Gestational age was based on the last menstrual period and confirmed by transvaginal US performed between 7 and 9 weeks' gestation. If the difference between the dates was greater than 5 days, the US data were used for dating. The date of ovum pickup was used for dating fetal gestation as 2 weeks 0 days if the woman conceived by embryo transfer after in vitro fertilization. In this study, women who conceived by various methods such as controlled ovarian stimulation, intrauterine insemination, and in vitro fertilization–embryo transfer with an ovulation-inducing drug were regarded as the ART subgroup, and women who spontaneously conceived, including those using timed coitus without controlled ovulation stimulation were categorized in the natural subgroup.

We analyzed demographic data and pregnancy outcomes between the adenomyosis and non-adenomyosis groups. The pregnancy outcome variables of this study (gestational age at delivery, preterm birth, birth weight, low birth weight, and mode of delivery) were compared between the subgroups. Preterm births were analyzed

with the use of 2 cutoff values defined as conventional preterm births before 37 gestational weeks and preterm births before 32 gestational weeks. Low birth weights were also analyzed with the use of 2 cutoff values defined as low birth weight of less than 2500 g and very low birth weight of less than 1500 g. Pregnancy outcomes of the study population were compared according to the presence of adenomyosis. Then, the adenomyosis and non-adenomyosis groups were subdivided into a natural subgroup and an ART subgroup, and pregnancy outcomes were compared respectively.

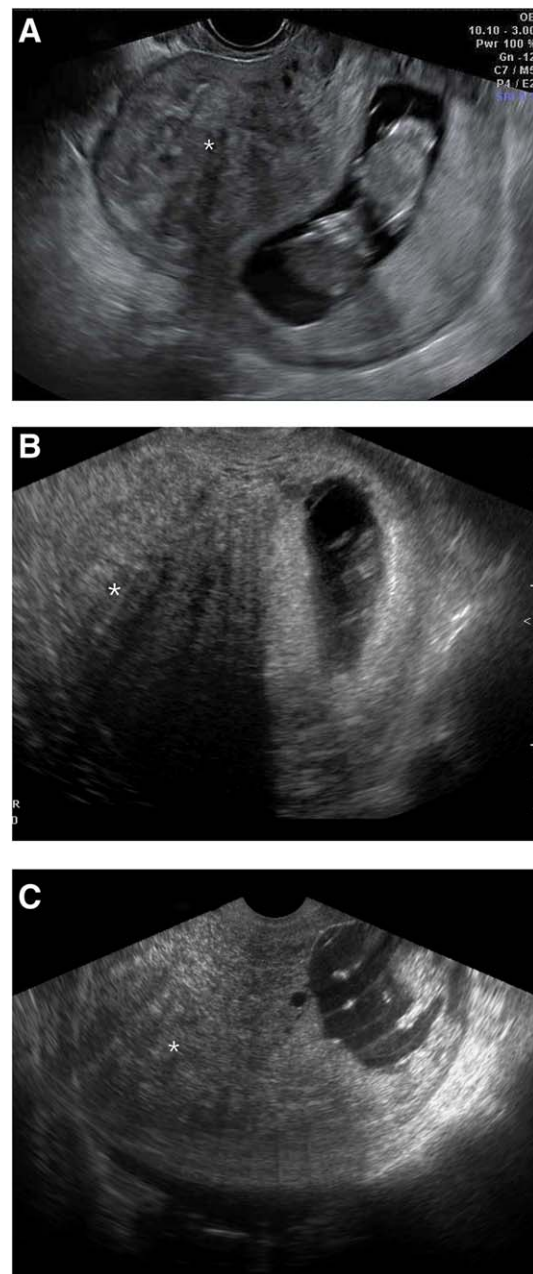
This study was approved by the Institutional Review Board at our hospital (CGH-IRB-2014-6). Statistical analyses were conducted with SPSS version 12.0 software (IBM Corporation, Armonk, NY). The data are presented as means  $\pm$  standard deviations and as numbers (percentage) for nominal and categorical variables. To assess differences between groups, the Student *t* test was used for assessment of continuous variables, and  $\chi^2$  and Fisher exact tests were used to detect differences in categorical variables. The odds ratio (OR) was used as a measure of the association between exposure covariates and preterm delivery. *P* < .05 was considered statistically significant.

## Results

A total of 11,173 consecutive pregnant women underwent first-trimester US during the study period. Of them, 88 (0.8%) women had a diagnosis of adenomyosis by transvaginal US in early pregnancy. An example of transabdominal US features of adenomyosis is shown in Figure 1. A globular and asymmetric enlarged uterus containing a poorly defined heterogeneous myometrial lesion is seen with the gestational sac. Sixteen cases were excluded from the analysis because of spontaneous abortion in 6 cases, intrauterine fetal death in 1 case, and follow-up loss in 9 cases. Therefore, a total of 72 (81.8%) pregnant women with adenomyosis who delivered in our institution were included in the adenomyosis group. Among the 11,085 women without adenomyosis, 8244 (74.4%) who delivered at our institution were included in the non-adenomyosis group. The remaining 2841 women were excluded from our study because they delivered at other regional hospitals, so we did not have information on their exact pregnancy outcomes.

Table 1 compares the maternal demographic characteristics and pregnancy outcomes for the adenomyosis

**Figure 1.** Adenomyosis with a gestational sac in early pregnancy on US. **A.** Globular enlarged uterus with a heterogeneous echo texture (asterisk) in the anterior corpus and an obscure endometrial/myometrial border at a gestational age of 11 weeks 4 days. **B.** Heterogeneous echo texture (asterisk) in the anterior corpus and an obscure endometrial/myometrial border at 11 weeks 4 days. **C.** Asymmetric, thickened, and poorly defined heterogeneous myometrial lesion with a focal adenomyoma (asterisk) in the anterior corpus and a gestational sac located in the lower uterine cavity at 11 weeks 1 day.



and non-adenomyosis groups. In the adenomyosis group, the mean maternal age at delivery was  $34.1 \pm 4.1$  years, and 65.3% of women were nulliparous; these values were higher than those in the non-adenomyosis group, but neither was statistically significant. However, we found that the adenomyosis group had significantly more infertile patients than the non-adenomyosis group. The ART subgroup was larger in the adenomyosis group: 34.7% (25 of 72) compared with only 2.3% (187 of 8244) in the non-adenomyosis group ( $P < .001$ ). The mean gestational age at delivery in the adenomyosis group was  $38.2 \pm 1.3$  weeks, which was 1 week earlier than that in the non-adenomyosis group ( $P < .05$ ). The mean birth weight of neonates was also significantly lower in the adenomyosis group than that in the non-adenomyosis group ( $P < .01$ ). However, the delivery modes were similar in both groups.

In Table 2, the risks of preterm birth and low birth weight according to presence of adenomyosis are presented. The risk of preterm birth before 37 and 32 weeks were significantly higher in the adenomyosis group than in the non-adenomyosis group (OR, 3.36; 95% confidence intervals [CI], 1.66–6.82;  $P < .001$ ; OR, 24.53; 95% CI, 9.12–66.02;  $P < .001$ , respectively). The risks of low-birth-weight and very low-birth-weight deliveries

were also significantly higher in the adenomyosis group (OR, 5.05; 95% CI, 2.56–9.97;  $P < .001$ ; OR, 15.54; 95% CI, 4.56–52.97;  $P < .001$ ).

Maternal characteristics and pregnancy outcomes according to the method of conception among women in the adenomyosis and non-adenomyosis groups are shown in Table 3. Among the women with adenomyosis, the numbers of preterm births and low birth weights were significantly higher in the ART subgroup than in the naturally conceived subgroup (28.0% versus 4.3%;  $P < .01$ ; 28.0% versus 6.4%;  $P < .05$ , respectively). However, in the non-adenomyosis group, the numbers of preterm births before 37 gestational weeks and low birth weights of less than 2500 g were not significantly different between the ART and naturally conceived subgroups (6.4% versus 4.0%;  $P > .05$ ; 4.8% versus 3.1%;  $P > .05$ ). In the ART group, 7 (28.0%) of 25 patients with adenomyosis and 12 (6.4%) of 187 patients without adenomyosis delivered before 37 weeks ( $P = .003$ ). However, in the spontaneous conception group, 2 (4.2%) of 47 women with adenomyosis and 324 (4.0%) of 8057 women without adenomyosis delivered before 37 weeks ( $P = .71$ ). Likewise, in the ART group, low birth weight was more prevalent in the women with adenomyosis than in the women without adenomyosis (7 of 25

**Table 1.** Comparison of Demographic Characteristics and Pregnancy Outcomes According to the Presence of Adenomyosis on US

Variable	Adenomyosis (n = 72)	Non-Adenomyosis (n = 8244)	P
Maternal age, y	34.1 ± 4.1	33.8 ± 3.6	.57
Nulliparous, n (%)	47 (65.3)	5,050 (61.3)	.54
Previous abortion, n (%)	35 (48.6)	3,150 (38.2)	.07
ART, n (%)	25 (34.7)	187 (2.3)	<.001
Gestational age at delivery, wk	38.2 ± 1.3	39.3 ± 1.4	.013
Preterm birth, n (%)	9 (12.5)	336 (4.1)	<.001
Birth weight, g	3108.6 ± 531.0	3266.2 ± 426.9	.003
Low birth weight, n (%)	10 (13.9)	255 (3.1)	<.001
Cesarean delivery, n (%)	28 (43.8)	2997 (36.4)	.24

**Table 2.** Comparison of the Incidence of Preterm Birth and Low Birth Weight According to the Presence of Adenomyosis on US

Variable	Adenomyosis (n = 72)	Non-Adenomyosis (n = 8244)	OR	95% CI	P
Preterm birth, n (%)					
<32 wk	5 (6.9)	25 (0.3)	24.53	9.12–66.02	<.001
<37 wk	9 (12.5)	336 (4.1)	3.36	1.66–6.82	<.001
Low birth weight, n (%)					
<1500 g	3 (4.2)	23 (0.3)	15.54	4.56–52.97	<.001
<2500 g	10 (13.9)	255 (3.1)	5.05	2.56–9.97	<.001

[28.0%] versus 9 of 187 [4.8%];  $P = .003$ ). However, in the spontaneous conception group, 3 (6.4%) of 47 patients with adenomyosis and 246 (3.1%) of 8057 patients without adenomyosis delivered low-birth-weight neonates ( $P = .175$ ).

Odds ratios of preterm birth and low birth weight according to conception method in the adenomyosis group are shown in Table 4. The risks of preterm birth before 37 gestational weeks and low birth weight were significantly higher in the ART subgroup than in the naturally conceived subgroup (OR, 8.75; 95% CI, 1.66–46.19;  $P = .007$ ; OR, 5.70; 95% CI, 1.33–24.55;  $P = .027$ , respectively).

## Discussion

This study found an approximately 3-fold increased risk of preterm births in women with adenomyosis, which increased to greater than 24-fold for preterm births before 32 gestational weeks. Azziz<sup>15</sup> reported 2 cases of pregnant women with adenomyosis in 1986, and only 29 reports of complications associated with adenomyosis in pregnancy were published during the 1980s.<sup>2</sup> These findings indicate that adenomyosis during pregnancy

was rarely diagnosed in early studies. Since then, with improved imaging techniques, 2 studies investigated the complications in pregnant women with adenomyosis.<sup>10,11</sup> Our study assessed the rate of preterm births with a comparison between adenomyosis and non-adenomyosis groups.

We used 2 cutoff values to distinguish early preterm birth (<32 gestational weeks) and conventional preterm birth (<37 gestational weeks) when analyzing the rates of preterm birth, because neonates born before 32 weeks are thought to have more neurologic sequelae.<sup>16</sup> To date, there are only a few studies regarding pregnancy with adenomyosis. Adenomyosis, which is more frequent in women in their fourth and fifth decades, is now being detected more often during pregnancy as a result of increased maternal age at pregnancy, owing to delayed marriage and childbearing, which is due in part to improvements in ART. However, a pregnant woman with adenomyosis who has conceived by ART is expected to have more complications than a woman who has spontaneously conceived. In this study, women with a diagnosis of adenomyosis during early pregnancy were more likely to have a history of infertility, and 34.7% of this group conceived by ART. We found that

**Table 3.** Comparison of Maternal Characteristics and Pregnancy Outcomes According to the Method of Conception

Variable	Adenomyosis		P	Non-Adenomyosis		P
	Natural (n = 47)	ART (n = 25)		Natural (n = 8057)	ART (n = 187)	
Maternal age, y	33.4 ± 4.1	35.5 ± 3.8	.039	33.7 ± 3.6	35.5 ± 3.3	<.001
Nulliparous, n (%)	28 (59.6)	19 (76.0)	.20	4909 (60.9)	141 (75.4)	<.001
Previous abortion, n (%)	19 (40.4)	16 (64.0)	.057	3076 (38.2)	74 (39.6)	.69
Gestational age at delivery, wk	38.9 ± 2.1	36.8 ± 4.6	.040	39.2 ± 1.3	39.0 ± 4.6	.05
Preterm birth, n (%)	2 (4.3)	7 (28.0)	.007	324 (4.0)	12 (6.4)	.10
Birth weight at delivery, g	3192.6 ± 476.7	2936.4 ± 603.8	.098	3267.5 ± 422.9	3209.1 ± 572.0	.166
Low birth weight, n (%)	3 (6.4)	7 (28.0)	.027	246 (3.1)	9 (4.8)	.193

**Table 4.** Comparison of Incidence of Preterm Birth and Low Birth Weight According to Conception Method Among Adenomyosis Group

Variable	Natural (n = 47)	ART (n = 25)	OR	95% CI	P
Preterm birth, n (%)					
<32 wk	1 (2.1)	4 (16.0)	8.76	0.92–83.24	.046
<37 wk	2 (4.3)	7 (28.0)	8.75	1.66–46.19	.007
Low birth weight, n (%)					
<1500 g	0 (0)	3 (12.0)	NA	NA	NA
<2500 g	3 (6.4)	7 (28.0)	5.70	1.33–24.55	.027

NA indicates not applicable.

US findings suggesting adenomyosis are associated with an increased risk of preterm delivery and low birth weight in women who conceived by ART but not in women who conceived spontaneously.

The primary strength of this study was the assessment of the rates of preterm birth and low birth weight according to the US findings of adenomyosis in a large population of consecutive pregnant women. The secondary strength was the subgroup analysis of the adenomyosis group according to the method of conception.

However, this study had several limitations. First, diagnosis of adenomyosis during pregnancy is difficult because of the enlarged uterus and the limitations of diagnostic tools and has the possibility of a selection bias. As most previous studies included women who underwent hysterectomy, the prevalence of adenomyosis in pregnancy was not widely studied.

In this study, the diagnosis of adenomyosis was made only by US. Transvaginal US is a noninvasive diagnostic tool for adenomyosis, with sensitivity and specificity reported to be 53% to 89% and 67% to 98%, respectively.<sup>17</sup> As a result, the overall prevalence of adenomyosis was about 0.8%, which was considerably lower than the rate of approximately 20% to 30% at hysterectomy reported in previous studies.<sup>2,18,19</sup> Ultrasonographic diagnosis can have limitations; therefore, a definitive diagnosis is only possible by histopathologic analysis. During pregnancy, other diagnostic tools such as computed tomography are not possible because of radiation hazards, and routine magnetic resonance imaging for adenomyosis is limited by the high cost. This study compared preterm birth rates in patients with US findings suggestive of adenomyosis in early pregnancy with those in patients without such findings. We did not perform a subgroup analysis according to specific US findings because of the low numbers in the study population.

Second, confounding factors for the reproductive outcomes of conditions such as endometriosis and leiomyomas were not analyzed. Those conditions commonly exist concomitantly with adenomyosis, and concomitant adenomyosis in the specimens of women who underwent hysterectomy have been found in 6% to 22% of patients with endometriosis and 35% to 55% of patients with leiomyomas.<sup>20</sup> However, it has been reported that myomas do not affect the rate of preterm delivery.<sup>21</sup> In addition, it is hard to diagnose endometriosis because pregnancy may temporarily relieve the

symptoms of endometriosis, and it is hard to do diagnostic laparoscopy, the preferred method for diagnosis of endometriosis, because of the pregnancy status.

In conclusion, the overall prevalence of adenomyosis during pregnancy was 0.8%; 12.5% of pregnant women with adenomyosis delivered before 37 gestational weeks; and 13.9% delivered low-birth-weight neonates of less than 2500 g. The US findings suggested that adenomyosis in early pregnancy had an association with increased risks of preterm delivery and low birth weight in women who conceived by ART but not in women who conceived spontaneously. Therefore, clinicians should be aware of the risk of preterm birth and low birth weight in pregnant women with adenomyosis, and especially meticulous attention should be paid to women who conceive by ART. However, further randomized controlled studies with more data are needed on this subject.

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