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Complications and outcomes of pregnant women with adenomyosis in Japan

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Abstract

Purpose: To investigate the impact of adenomyosis on the complications and outcomes of pregnancy in Japan.

Methods: We carried out a multicenter retrospective questionnaire survey. A questionnaire regarding pregnancy complications and the outcomes of pregnancy was sent to 725 facilities.

Results: Data were obtained on the cases of 272 pregnant women with adenomyosis from 65 facilities. The complications of pregnancy included miscarriage before 12 weeks of pregnancy (14.8%), miscarriage after 12 weeks of pregnancy (9.9%), preterm delivery (24.4%), fetal growth restriction (11.8%), pregnancy-induced hypertension (9.9%), intrauterine infection (7.3%), and cervical incompetency (5.3%). The rates of pregnancy complications in the three groups classified according to pretreatment for adenomyosis (no pretreatment, medication, surgery) did not differ to a statistically significant extent. The rates of miscarriage (>12 weeks) and cervical incompetency increased according to the size of the adenomyosis. The rates of pregnancy-induced hypertension and uterine infection in patients with diffuse-type adenomyosis were higher than that in patients with focal-type adenomyosis.

Conclusions: Our results show that the increased size and diffuse type of adenomyosis are associated with adverse pregnancy outcome. We should be aware of the higher incidence of pregnancy-induced hypertension and uterine infection in patients with diffuse-type adenomyosis.

KEYWORDS

adenomyosis, complication, miscarriage, pregnancy, preterm delivery

1 | INTRODUCTION

The frequency of adenomyosis in pregnancy has been increasing in recent years, along with the increase in the number of pregnancies in women of advanced age and the increase in pregnancies achieved by fertility treatments.[1] Adenomyosis has been reported to be associated with poor pregnancy outcomes, including an increased risk of preterm delivery, preterm premature rupture of membranes (PPROM), and fetal growth restriction (FGR).[2,3] However, the potential impact of adenomyosis on the outcomes of pregnancy is still unclear, because few studies have addressed the associations between adenomyosis and pregnancy outcomes, and because the study populations of those studies were small.

Adenomyosis is a benign lesion of myometrial tissue that is characterized by the presence of endometrial glands and stroma within

the myometrium. During pregnancy, the invasion of trophoblasts into the endometrium and the myometrial junctional zone causes decidualization and unique vascular changes.[4] The thickening and disruption of the junctional zone in women with adenomyosis might be associated with placental insufficiency and complications of pregnancy. In addition, the type of adenomyosis is considered to be an important factor affecting decidualization and placentation. Adenomyosis can be classified into two categories: (1) focal adenomyosis, in which the area of hypertrophic and distorted endometrium and myometrium is restricted (usually embedded within the myometrium), and (2) diffuse adenomyosis, which is the extensive form of the disease, and which is characterized by foci of endometrial mucosa (glands and stroma) scattered throughout the uterine musculature.[5] At present, no data are available for analyzing the relationship between the type of adenomyosis and the outcomes of pregnancy.

In order to investigate the current clinical status of adenomyosis, we carried out a nationwide survey in Japan. A multicenter retrospective survey of pregnant patients with adenomyosis was carried out to show the complications and outcomes of pregnancy in Japan.

2 | METHODS

We carried out a nationwide survey between October, 2011 and March, 2012 to evaluate the involvement of adenomyosis in pregnancy outcomes as an official project of the Japan Society of Obstetrics and Gynecology. A retrospective survey was carried out. A questionnaire was sent to 725 Japanese medical facilities that are authorized as training facilities by the Japan Society of Obstetrics and Gynecology. The questionnaire, which was mailed to all facilities, sought the cooperation of the facilities in carrying out this survey. The retrospective analysis was based on the clinical records of each facility.

The questionnaire inquired about the outcomes of pregnancy in women with adenomyosis. To analyze the impact of adenomyosis on pregnancy complications, the questionnaire inquired about information related to adenomyosis, including the methods by which it was diagnosed, size (major axis), type (focal or diffuse), localization (anterior wall or posterior wall), pretreatment before pregnancy (medication, conservative operation, no pretreatment), and pregnancy complications. In this study, cervical incompetency was diagnosed as cervical dilatation without uterine contraction, which is clearly different from late miscarriage with cervical dilatation and uterine contractions.

Cases involving patients with myoma of the uterus and endometriosis were excluded from the analysis, in order to eliminate the influence of these diseases on pregnancy complications. The diagnosis of adenomyosis was made by a gynecologist at each facility based on imaging studies, including ultrasonography and/or magnetic resonance imaging. The questionnaire was collected and analyzed at the Department of Obstetrics & Gynecology, Yamaguchi University Graduate School of Medicine, Ube, Yamaguchi, Japan.

The results were analyzed using the SPSS 13.0 for Windows software program (SPSS, Chicago, IL, USA). The Mann-Whitney *U*-test, Mann-Whitney *U*-test with the Bonferroni correction, Kruskal–Wallis *H*-test, Fisher's test and Pearson's chi-squared test were used as appropriate. *P*-values of $< .05$ were considered to show statistical significance.

3 | RESULTS

The questionnaire, which was sent to 725 facilities in Japan, was completed by 65 facilities. The responses included data on 272 pregnant women with adenomyosis. A total of 10 cases were excluded due to insufficient data. Thus, a total of 262 cases were analyzed in the present study. Among the 262 cases, 69 (26.3%) were diagnosed with adenomyosis based on transvaginal ultrasound and magnetic resonance imaging, while the others (73.7%, n = 193) were diagnosed based on transvaginal ultrasound alone. A total of 33 cases received medications (gonadotropin-releasing hormone agonist, n = 28; low-dose estrogen–progestin, n = 5; danazol, n = 5; dienogest, n = 2), and 24 cases underwent surgery (laparoscopic operation, n = 7; laparotomy, n = 5; unknown, n = 12) as pretreatment for adenomyosis, whereas 205 cases received no pretreatment before pregnancy (Fig. 1). The patients in the no pretreatment and medication group became pregnant with lesions of adenomyosis, whereas the patients of the surgery group became pregnant without lesions.

Among the 262 cases of pregnancy with adenomyosis, complications of pregnancy occurred in 189 (72.1%) cases, including miscarriage before 12 weeks of pregnancy (14.8%, 38/262), miscarriage after 12 weeks of pregnancy (9.9%, 26/262), preterm delivery (24.4%, 64/262), FGR (11.8%, 31/262), PIH (9.9%, 26/262), intrauterine infection (7.3%, 19/262), cervical incompetency (5.3%, 14/262), PPROM (4.6%, 12/262), placenta previa (2.7%, 7/262), atonic bleeding (1.5%, 4/262), intrauterine fetal death (1.5%, 4/262), uterine rupture (0.4%, 1/262), and abruptio placentae (0.4%, 1/262; Table 1). With the exception of uterine infection (highly prevalent in the medication group), the rates of pregnancy complications did not differ to a statistically significant extent among the three groups (no pretreatment, medication, and surgery; Table 1).

To analyze the relationship between the size of the adenomyosis and the complications of pregnancy, we divided the cases into three groups according to the size of the focus: <40 mm, 40-60 mm, and >60 mm (Table 2). The miscarriage rates at >12 weeks in the <40 mm, 40-60 mm, and >60 mm groups were 7.1% (3/42), 3.6% (2/56), and 21.7% (10/46), respectively, whereas the cervical incompetency rates were 0.0% (0/42), 3.6% (2/56), and 15.2% (7/46), respectively. With the exception of the rates of miscarriage and cervical incompetency, which were higher in the >60 mm group, there were no significant differences in the other pregnancy complication rates of the three groups (Table 2).

To analyze whether different types of adenomyosis influence pregnancy complications, the patients were divided into two groups according to the type of adenomyosis: 99 patients had focal-type adenomyosis (adenomyoma), and 138 had diffuse-type adenomyosis (Table 3). In patients with focal-type adenomyosis, the rates of miscarriage before and after 12 weeks of pregnancy were 15.2% (15/99) and

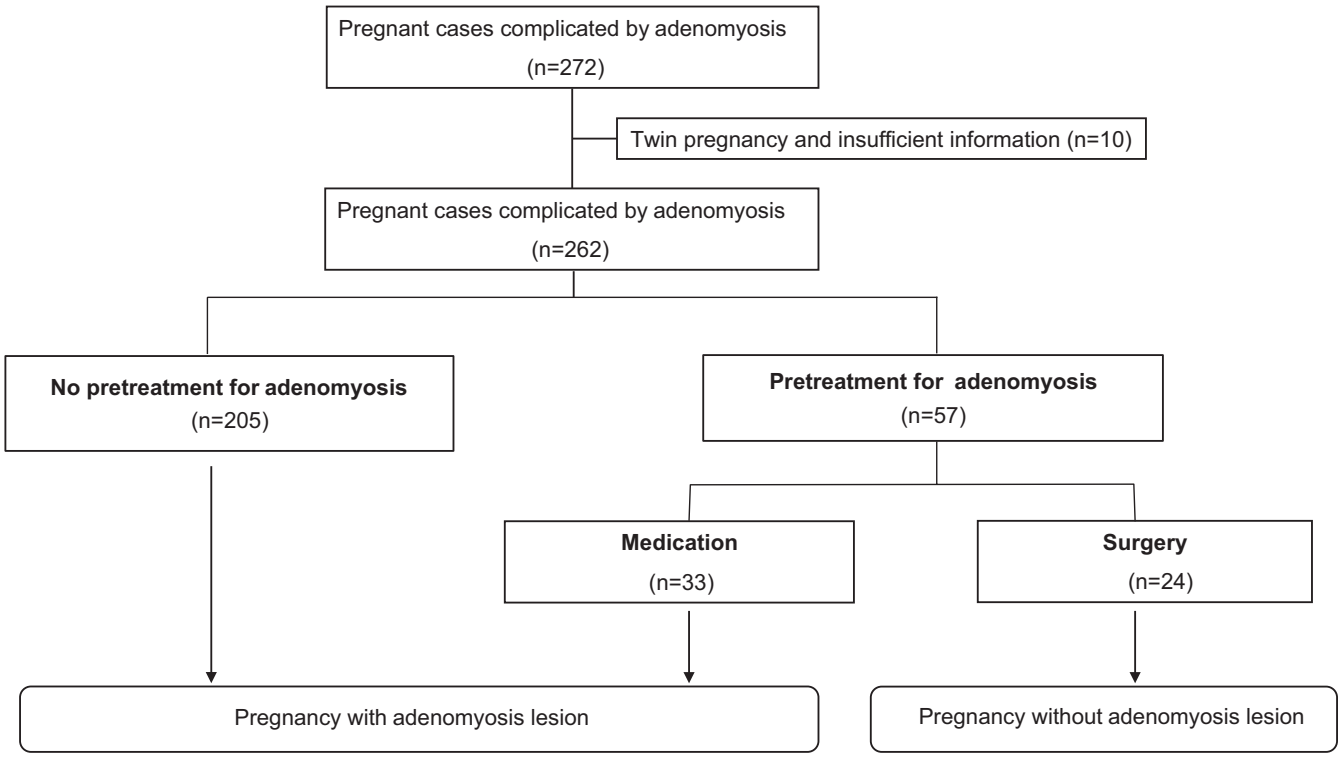

FIGURE 1 A flow diagram of the pregnant women with adenomyosis

TABLE 1 Clinical complications of pregnant women with adenomyosis and the impact of pretreatment for adenomyosis

	Total	No pretreatment	Medication	Surgery	*P*
No. pregnant women	262	205	33	24	
Age (years)	34.8 ± 4.3	34.8 ± 4.2	35.0 ± 4.3	35.2 ± 4.8	NS
Miscarriage	64 (24.4%)	51 (24.9%)	8 (24.8%)	5 (20.8%)	NS
<12 weeks	38 (14.5%)	31 (15.1%)	4 (12.1%)	3 (12.5%)	NS
>12 weeks	26 (9.9%)	20 (9.8%)	4 (12.1%)	2 (8.3%)	NS
Premature labor	64 (24.4%)	49 (23.9%)	11 (33.3%)	4 (16.7%)	NS
Fetal growth restriction	31 (11.8%)	29 (14.1%)	2 (6.1%)	0 (0.0%)	NS
Pre-eclampsia	26 (9.9%)	22 (10.7%)	4 (12.1%)	0 (0.0%)	NS
Cervical incompetency	14 (5.3%)	9 (4.4%)	3 (9.1%)	2 (8.3%)	NS
Uterine infection	19 (7.3%)	12 (5.9%)	7 (21.2%)	0 (0.0%)	< .05
IUFD (>22 weeks)	4 (1.5%)	3 (1.5%)	1 (3.0%)	0 (0.0%)	NS
Placenta previa	7 (2.7%)	5 (2.4%)	1 (3.0%)	1 (4.2%)	NS
PPROM	12 (4.6%)	12 (5.9%)	0 (0.0%)	0 (0.0%)	NS
Atonic bleeding	4 (1.5%)	3 (1.5%)	1 (3.0%)	0 (0.0%)	NS
Uterine rupture	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (4.2%)	NS
Abruptio placentae	1 (0.4%)	0 (0.0%)	1 (3.0%)	0 (0.0%)	NS
Amniotic fluid embolism	1 (0.4%)	0 (0.0%)	1 (3.0%)	0 (0.0%)	NS
Severe emesis	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (4.2%)	NS
Neonatal death	3 (1.1%)	3 (1.5%)	0 (0.0%)	0 (0.0%)	NS

The age is shown as the mean ± SD. IUFD, intrauterine fetal death; NS, not significant; PPROM, preterm premature rupture of membranes.

9.1% (9/99), respectively. Similarly, the rates of miscarriage before and after 12 weeks of pregnancy in patients with diffuse-type adenomyosis were 15.2% (21/138) and 10.9% (15/138), respectively. Thus, the type of adenomyosis did not affect the rate of miscarriage. The rate of premature delivery in patients with diffuse-type adenomyosis (27.5%; 38/138) was higher than that in patients with focal-type adenomyosis

TABLE 2 Relationship between size of adenomyosis and clinical complications of pregnant women

	Size of adenomyosis (major axis)			
	<40 mm	40-60 mm	>60 mm	*P*
No. pregnant women	42	56	46	
Miscarriage	7 (16.7%)	13 (23.2%)	13 (28.3%)	NS
<12 weeks	4 (9.5%)	11 (19.6%)	3 (6.5%)	NS
>12 weeks	3 (7.1%)	2 (3.6%)	10 (21.7%)	< .05
Premature labor	10 (23.8%)	12 (21.4%)	14 (30.4%)	NS
Fetal growth restriction	3 (7.1%)	11 (19.6%)	6 (13.0%)	NS
Pre-eclampsia	2 (4.8%)	3 (5.4%)	5 (10.9%)	NS
Cervical incompetency	0 (0.0%)	2 (3.6%)	7 (15.2%)	< .05
Uterine infection	2 (4.8%)	4 (7.1%)	8 (17.4%)	NS
IUFD (>22 weeks)	0 (0.0%)	1 (1.8%)	1 (2.2%)	NS
Placenta previa	2 (4.8%)	1 (1.8%)	1 (2.2%)	NS
PPROM	3 (7.1%)	4 (7.1%)	2 (4.3%)	NS
Atonic bleeding	1 (2.4%)	1 (1.8%)	1 (2.2%)	NS
Uterine rupture	0 (0.0%)	0 (0.0%)	0 (0.0%)	NS
Abruptio placentae	0 (0.0%)	1 (1.8%)	0 (0.0%)	NS
Amniotic fluid embolism	0 (0.0%)	0 (0.0%)	0 (0.0%)	NS
Severe emesis	0 (0.0%)	0 (0.0%)	0 (0.0%)	NS
Neonatal death	1 (2.4%)	1 (1.8%)	1 (2.2%)	NS

IUFD, intrauterine fetal death; NS, not significant; PPROM, preterm premature rupture of membranes.

(19.2%, 19/99), but the difference was not statistically significant. The rate of PIH in patients with diffuse-type adenomyosis (13.8%; 19/138) was higher than that in patients with focal-type adenomyosis (5.1%; 5/99). The rate of intrauterine infection in patients with diffuse-type adenomyosis (10.9%; 15/138) was higher than that in patients with focal-type adenomyosis (2.0%; 2/99). The rates of the other complications of pregnancy did not differ to a statistically significant extent between these two groups (Table 3).

TABLE 3 Impact of the type of adenomyosis on clinical complications of pregnant women

	Focal type	Diffuse type	
	(n = 99)	(n = 138)	*P*
Miscarriage	24 (24.2%)	36 (26.1%)	NS
<12 weeks	15 (15.2%)	21 (15.2%)	NS
>12 weeks	9 (9.1%)	15 (10.9%)	NS
Premature labor	19 (19.2%)	38 (27.5%)	NS
Fetal growth restriction	12 (12.1%)	17 (12.3%)	NS
Pre-eclampsia	5 (5.1%)	19 (13.8%)	< .05
Cervical incompetency	5 (5.1%)	6 (4.3%)	NS
Uterine infection	2 (2.0%)	15 (10.9%)	< .05
IUFD (>22 weeks)	0 (0.0%)	3 (2.2%)	NS
Placenta previa	4 (4.0%)	2 (1.4%)	NS
PPROM	4 (4.0%)	5 (3.6%)	NS
Atonic bleeding	1 (1.0%)	2 (1.4%)	NS
Uterine rupture	0 (0.0%)	1 (0.7%)	NS
Abruptio placentae	0 (0.0%)	1 (0.7%)	NS
Amniotic fluid embolism	0 (0.0%)	0 (0.0%)	NS
Severe emesis	0 (0.0%)	1 (0.7%)	NS
Neonatal death	2 (2.0%)	0 (0.0%)	NS

IUFD, intrauterine fetal death; NS, not significant; PPROM, preterm premature rupture of membranes.

4 | DISCUSSION

This is the first study to report the results of a large-scale nationwide survey on the relationship between adenomyosis and the outcomes of pregnancy. Our results show that the increased size of adenomyosis is associated with miscarriage (>12 weeks) and cervical incompetency, and that the diffuse type of adenomyosis is related to pre-eclampsia and uterine infection. Miscarriage at >12 weeks and cervical incompetency were correlated with the size of the adenomyosis. In addition, the prevalence of PIH and uterine infection in patients with diffuse-type adenomyosis was high in comparison to patients with focal-type adenomyosis. Previous studies have reported on pregnancy complications in women with adenomayosis; however, the majority of these reports have been limited to small-scale studies and case reports. The rates of concomitant pathological conditions, including leiomyoma (35%-55%) and endometriosis (6%-20%), might drastically influence

the fertility of women with adenomyosis.[6-9] Chronic inflammation caused by endometriosis might be related to preterm delivery.[10] The presence of leiomyoma has been linked to an increased risk of spontaneous abortion, fetal malpresentation, placenta previa, preterm birth, cesarean section, and peripartum hemorrhage.[11] Thus, women with endometriosis and leiomyoma were excluded from this study.

In the present study, the incidence of miscarriage (24.4%; 64/262), especially miscarriage after 12 weeks of pregnancy (9.9; 26/262), was observed in pregnant women with adenomyosis. Consistent with our results, high rates of miscarriage in pregnant women with adenomyosis were reported by Youm (adenomyosis: 31.8% [21/66] vs control: 12.5% [29/224]), and Martinez-Conejero (adenomyosis: 32.8% [43/131] vs control: 16.3% [24/147]).[12,13] A recent report also showed a marked increase in the incidence of second trimester miscarriage (12.2%; 6/49) in pregnancies complicated by adenomyosis.[14] Patients with adenomyosis also show high levels of inflammatory substances, such as prostaglandins, which have been suggested as potential causes of uterine contraction.[2] Cyclooxygease-2, the rate-limiting enzyme that catalyzes the initial step in the formation of prostaglandins, is shown to be overexpressed in patients with adenomyosis.[15] In addition to prostaglandins, the production of pro-inflammatory cytokines including interleukin-1β, tumor necrosis factor-α, and epidermal growth factor is increased in the endometrium of women with adenomyosis.[16,17] In contrast, adenomyosis impairs the function of the myometrium. A recent report showed a significant increase in the myometrial stiffness (estimated with shear wave elastography) in patients with adenomyosis.[18] In fact, the intrauterine pressure has been reported to be increased in pregnant women with adenomyosis.[7,19] The uterine contractions caused by chronic inflammation and a high intrauterine pressure caused by myometrial stiffness might be factors that contribute to adenomyosis-related miscarriage and cervical incompetency.

The present results showed the incidence of preterm delivery (24.4%; 64/262) in pregnant women with adenomyosis. Consistent with our results, the increased incidence of preterm delivery in pregnant women with adenomyosis has been reported to range from 24.4% to 41.7%.[3] A case–control study also showed a significant (nearly twofold) increase in the risk of preterm delivery in women with adenomyosis.[2] In the present study, the incidence of PPROM (4.6%; 12/262), which is the most important cause of preterm delivery, was high in comparison with the overall prevalence of PPROM (2.8%; 6902/242 715), which was determined using the Perinatal Database of the Japan Society for Obstetrics and Gynecology.[20] The chronic inflammation and high intrauterine pressure in pregnant women with adenomyosis might be risk factors for PPROM and preterm delivery.

In the present study, the incidence of PIH in pregnant women with adenomyosis (9.9%; 26/262) was high. It is significantly higher than the reported prevalence in Japanese women (3.04%; 7371/242 715).[20] During pregnancy, the invasion of trophoblasts to the endometrium and the myometrial junctional zone causes decidualization and unique vascular changes.[4] The impaired decidualization of the myometrial spiral arteries is a predisposing factor for failed intravascular trophoblast invasion.[21] Defective deep placentation has been reported to be associated with a spectrum of obstetric complications, including late miscarriage, preterm labor, FGR, and pre-eclampsia.[22] As the thickening and disruption of the junctional zone appearance is strongly associated with uterine adenomyosis, adenomyosis might be related to placental insufficiency and poor placental perfusion, resulting into PIH.[4] Our results also showed that the incidence of FGR (11.8%; 31/262) was higher than that reported in the general population (5%-10%).[23] FGR cases of adenomyosis-complicated pregnancy with poor placental blood flow were reported.[24] The impaired deep placentation and PIH in pregnant women with adenomyosis might be involved in the increased incidence of FGR.

The functional changes that occur as a result of adenomyosis during pregnancy and after delivery include decidualization and hemorrhage within the adenomyosis. As adenomyosis is characterized by a chronic inflammatory disease, it could be responsible for severe infection and abscess formation within the adenomyotic foci.[25,26] The present results show an increase in the incidence of intrauterine infection (7.3%; 19/262) in pregnant women with adenomyosis. Hysterectomy was necessary in two women as a result of severe infection, and septic abortion and postpartum abscess formation, respectively (data were not shown). Adenomyosis can be associated with inflammatory consequences, such as septic abortion, preterm delivery, and abscess formation in pregnant women.

No reports have evaluated whether medication or surgical management for adenomyosis influence the complications of pregnancy. The advantages of removing the affected area must be balanced against the disadvantages of leaving a possibly defective uterine wall. Thus, there is a recognized difficulty in establishing the optimum conservative surgical technique for adenomyosis, and several strategies have been proposed, including different operative options (open, laparoscopic), surgical techniques (adenomyomectomy: complete excision, cytoreductive surgery: partial adenomyomectomy), and modified surgical techniques (U-shaped suturing, overlapping flaps, triple-flap method, and transverse H incision).[27-30] In the present study, there were no data to suggest that conservative surgery as a pretreatment for adenomyosis before pregnancy reduced the incidence of pregnancy complications. However, as the surgical techniques differed by facility, it is difficult to analyze the association between the pregnancy outcomes and the individual surgical techniques.

Although a large lesion of adenomyosis is likely to be associated with a poor pregnancy outcome, there are no data to assess the relationship between the size of the lesion and pregnancy complications. In the present study, we measured the lesions at the major axis of the focus, to provide a simple and objective measurement for both focal-type and diffuse-type adenomyosis. The miscarriage rates (>12 weeks) and the cervical incompetency rates were higher in pregnant women with large lesions (>60 mm). It is possible that miscarriage and cervical incompetency are caused by the increased inflammation and high intrauterine pressure in women with large lesions of adenomyosis.

Another important finding of the present study was the relationship between the type of adenomyosis and pregnancy complications. The rates of PIH and intrauterine infection in patients with diffuse-type adenomyosis were higher than those in patients with focal-type

adenomyosis. Previous reports have also shown that diffuse-type adenomyosis is more common than focal-type adenomyosis. In one study, the prevalence of diffuse-type and focal-type adenomyosis was 81.7% and 18.3%, respectively,[31] in another, it was 66.7% and 33.3%, respectively.[32] In the present survey, 58.2% (138/237) of the pregnancies involved diffuse-type adenomyosis. Diffuse adenomyosis is associated with various findings, including the enlargement of the uterus involving the entire myometrium in the posterior and/or anterior wall and junctional zone thickening. As diffuse thickening of the junctional zone, as well as of the whole myometrium, is a possible cause of the modification of the interface between the endometrium and myometrium, it is possible that impaired decidualization and defective deep placentation are more severe in cases of diffuse-type adenomyosis than in cases of focal-type adenomyosis. It should be noted that our results showed a high incidence of PIH in pregnant women with diffuse-type adenomyosis.

The present results indicate that the increased size of adenomyosis is associated with miscarriage (>12 weeks) and cervical incompetency, and that the diffuse type of adnomyosis is related to pre-eclampsia and uterine infection. We should be aware of these potential complications of adenomyosis in pregnancy. Our study also showed that the incidence of PIH and uterine infection was higher in patients with diffuse-type adenomyosis. We believe that this study provides information that will be useful in the management of pregnant women with adenomyosis.

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DISCLOSURES

Conflict of interest: The authors declare no conflict of interest. *Human and Animal Rights:* The study protocol was reviewed and approved by the institutional review board of Yamaguchi University Graduate School of Medicine (No H23-67). This article does not contain any study with animal participants that have been performed by any of the authors.

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