Received: 17 March 2017 | Accepted: 15 April 2017

DOI: 10.1002/rmb2.12036

ORIGINAL ARTICLE

WILEY Reproductive Medicine and Biology

Clinical outcomes of infertility treatment for women with adenomyosis in Japan

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Funding information
JSOG

Abstract

Aim: A multicenter, retrospective survey was conducted in order to investigate the current clinical status of adenomyosis in Japan.

Methods: The questionnaires covered the management of infertile women with adenomyosis and the outcomes of infertility treatment in women with adenomyosis. The questionnaires were sent to 1149 facilities in Japan.

Results: The data were obtained on 535 infertile women with adenomyosis from 190 facilities. Regarding management, infertility treatment was performed without pretreatment for adenomyosis in 37 facilities, after medication in eight facilities, and after an operation in four facilities. Management policies were not established in 106 facilities. Regarding outcomes, the pregnancy rate was 41.7% and the abortion rate was 29.8%. Eighty-five patients received medication and 89 patients underwent surgery as a pretreatment before infertility treatment, while 361 patients had no pretreatment. In relation to the type of adenomyosis, 162 patients had the focal type and 336 patients had the diffuse type. The pregnancy rate and abortion rate were not affected by pretreatment or the type of adenomyosis.

Conclusion: The management policy for infertile women with adenomyosis has not been established. The pregnancy rate of infertility treatment is about 40%. There were no data to suggest that medication or surgery as a pretreatment for adenomyosis increased the pregnancy rate in infertile women.

KEYWORDS

adenomyosis, infertility, miscarriage, pregnancy rate, surgery

1 | INTRODUCTION

Advanced age is a major risk factor for adenomyosis. As many women delay seeking conception, they are more commonly diagnosed with adenomyosis during the later stages of reproductive age.[1,2] Recent advances in imaging methods using transvaginal ultrasonography and magnetic resonance imaging (MRI) have enabled a more detailed evaluation of the uterine muscle for the diagnosis of women with adenomyosis.[3,4]

Destruction of the normal architecture of the myometrium, leading to impairment of the uterine mechanisms, has been proposed as a mechanism by which adenomyosis causes infertility.[5,6] While some groups report that adenomyosis negatively impacts the outcomes of infertility treatment,[7-10] others have not found any such negative association.[11-14] There is a lack of consensus in the literature regarding the relationship between adenomyosis and fertility. As the available data on the relationship between adenomyosis and infertility are still scant

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and limited to small-scale cases, the impact of adenomyosis on female fertility is still unclear.

Although substantial effort has been focused on improving the reproductive outcomes by pretreatment for adenomyosis, there is presently no evidence to suggest the potential benefit of medication or surgical intervention, in terms of the fertility prognosis.[15] Multiple treatment modalities, including hormonal therapy with gonadotropin-releasing hormone (GnRH) agonists and conservative surgical procedures, for women with adenomyosis have been used to restore their fertility. Although successful pregnancies after prolonged down-regulation with GnRH agonists[16,17] and conservative surgery have been reported,[18-20] there is no agreement on the most appropriate therapeutic method for managing infertile patients with adenomyosis.

In addition, the size and type of adenomyosis are considered to be important factors that affect fertility. Adenomyosis can be classified into two categories: focal adenomyosis, which is a restricted area of hypertrophic and distorted endometrium and myometrium, usually embedded within the myometrium; and diffuse adenomyosis, which is the extensive form of the disease, characterized by foci of endometrial mucosa (glands and stroma) scattered throughout the uterine musculature.[21] There are presently no available data to analyze the relationship between the type of adenomyosis and infertility.

In order to investigate the current clinical status of adenomyosis in Japan, a nationwide survey was conducted. A multicenter, retrospective survey of infertility patients with adenomyosis was performed to demonstrate the prevalence, clinical features, treatments, and outcomes of infertility therapy in women with adenomyosis in Japan.

2 | MATERIALS AND METHODS

Between October, 2011 and March, 2012 a nationwide survey was conducted in order to evaluate the impact of adenomyosis on infertility treatment and pregnancy outcomes as an official project of the Japan Society of Obstetrics and Gynecology (JSOG). A retrospective survey was performed by using questionnaires that were sent to 1149 Japanese medical facilities, including 725 institutes that were authorized as training facilities by JSOG and 582 institutes that were registered to JSOG for assisted reproductive technology (ART). Two questionnaires were mailed to all the facilities seeking their cooperation for this survey in order to perform a retrospective analysis based on the clinical records of each facility.

Questionnaire 1 inquired about the management policy for infertile women with adenomyosis and Questionnaire 2 inquired about the outcomes of infertility treatment in women with adenomyosis. In order to investigate the management policy of each facility for infertile women with adenomyosis, Questionnaire 1 inquired about the strategy for infertility treatment, including no pretreatment or the application of medication, a conservative operation, uterine artery embolization, and others before infertility treatment, or no established strategy (dependent on the individual situation). In order to analyze the impact of adenomyosis on infertility treatment, Questionnaire 2 inquired about the number of infertility patients with adenomyosis, methods of the diagnosis, size (major axis), type (focal or diffuse), localization (anterior wall or posterior wall), infertility treatment, and outcome of the infertility treatments. Questionnaire 2 also assessed any pretreatment for adenomyosis before infertility treatment.

In this survey, patients with myoma of the uterus and endometriosis were excluded in order to eliminate the influence of these diseases on fertility. The diagnosis of adenomyosis was made by the gynecologist of each facility with imaging modalities, including ultrasonography and/or MRI. The questionnaires were collected and analyzed at the Department of Obstetrics and Gynecology, Yamaguchi University Graduate School of Medicine, Ube, Japan.

A statistical analysis was carried out with SPSS for Windows, v. 13.0 (SPSS Inc., Chicago, IL, USA). The Mann-Whitney *U*-test, Mann-Whitney *U*-test using the Bonferroni correction, Kruskal-Wallis *H*-test, Fisher's test or Pearson's chi-square test were employed as appropriate. Differences were considered to be significant if $P<.05$.

3 | RESULTS

The questionnaires were sent to 1149 facilities in Japan and were filled out by 190 facilities (response rate: 16.5%).

3.1 | Questionnaire 1

The Questionnaire 1 results were obtained from 155 facilities (Table 1). Of the 155 facilities, infertility treatment was performed without any pretreatment for adenomyosis in 37 facilities (23.9%). Infertility treatment was performed after medication for adenomyosis in eight facilities (5.2%) and the medications were as follows: GnRH agonists in six facilities and Dienogest in two facilities. Infertility treatment was performed after an operation in four facilities (2.6%) and management policies were not established (dependent on individual situations) in 106 facilities (68.4%).

3.2 | Questionnaire 2

The Questionnaire 2 results were obtained from 190 facilities, with data on 535 infertile women with adenomyosis. Of the 535 patients, 23.9%

TABLE 1 Management policy of infertile women with adenomyosis in Japan

Pretreatment	Facilities (N)	(%)
None	37	23.9 (37/155)
Medication	8	5.2 (8/155)
GnRH agonist	6	–
Dienogest	2	–
Conservative surgery	4	2.6 (4/155)
UAE	0	0 (0/155)
Not established (depends on individual situation)	106	68.4 (106/155)

GnRH, gonadotropin-releasing hormone; UAE, uterine artery embolization.

TABLE 2 The impact of pretreatments for adenomyosis before infertility treatment on clinical outcomes

	Total	No pretreatment	Medication (GnRHa, Dienogest)	Conservative surgery	*P*
Number of patients	535	361	85	89	
Age	35.5±4.4	35.9±4.5	34.8±4.4	34.8±4.2	NS
Pregnancy rate (%)	41.7% (223/535)	41.3% (149/361)	43.5% (37/85)	41.6% (37/89)	NS
Miscarriage (%)	29.8% (75/252)	30.3% (50/165)	31.7% (13/41)	26.1% (12/46)	NS
Non-ART (n)	240	146	47	47	–
Pregnancy rate (%)	37.5% (90/240)	41.0% (60/146)	36.1% (17/47)	27.7% (13/47)	NS
Miscarriage (%)	21.1% (20/95)	22.6% (14/62)	5.9% (1/17)	33.3% (5/15)	NS
ART (n)	295	215	38	42	
Pregnancy rate (%)	44.4% (131/295)	41.4% (89/215)	52.6% (20/38)	57.1% (24/42)	NS
Miscarriage (%)	34.3% (54/157)	34.0% (35/103)	52.2% (12/23)	22.6% (7/31)	NS

Data are shown as the mean ± standard deviation. ART, assisted reproductive technology; GnRHa, gonadotropin-releasing hormone agonist.

TABLE 3 Relationship between the size of the adenomyosis and the clinical outcome of the infertility treatment

	Size of the adenomyosis (major axis)				
Characteristic	<40 mm	40-60 mm	60-80 mm	>80 mm	*P*-value
Number of patients	121	88	38	29	–
Pregnancy (%, N)	41.3 (50/121)	34.1 (30/88)	44.7 (17/38)	31.0 (9/29)	NS
Miscarriage(%, N)	25.0 (14/56)	32.3 (10/31)	36.4 (8/22)	33.3 (3/9)	NS

(128) were diagnosed with adenomyosis by transvaginal ultrasound and MRI, while the others (76.1%, n=407) were diagnosed by transvaginal ultrasound only. The pregnancy rate (number of women achieving pregnancies/total number of women) was 41.7% and the miscarriage rate (number of abortions/total number of pregnancies) was 29.8%. A total of 295 patients had received ART, whereas 240 had received the usual infertility treatment without ART. The pregnancy rate and miscarriage rate by the usual infertility treatment without ART were 37.5% (90/240) and 21.1% (20/90), respectively, whereas the rate was 44.4% (131/295) and 34.3% (54/157) by ART, respectively (Table 2).

Eighty-five patients received medications (GnRH agonists in 67, low-dose estrogen–progestin in 12, Danazol in seven, Dienogest in four) and 89 patients underwent surgery (laparoscopic operation in 24, laparotomy in 65) as a pretreatment before the fertility treatment, while 361 patients had no pretreatment. The pregnancy rate (no treatment: 41.3%; medication: 43.5%; operation: 41.5%) and miscarriage rate (no treatment: 30.3%; medication: 31.7%; operation: 26.1%) were not affected by pretreatment for adenomyosis (Table 2).

In order to analyze the relationship between the size of the adenomyosis and the clinical outcomes in women with infertility treatment, the women were divided into four groups (<40 mm, 40-60 mm, 60-80 mm, >80 mm), depending on the size of the focus. The pregnancy rates were 41.3% (50/121), 34.1% (30/88), 44.7% (17/38), and 31.0% (9/29), respectively, and the miscarriage rates were 25.0% (14/56), 32.3% (10/31), 36.4% (8/22), and 33.3% (3/9) for the < 40 mm, 40-60 mm, 60-80 mm, and >80 mm groups, respectively. There were no significant differences in the pregnancy and miscarriage rates among the four groups (Table 3).

The women were subdivided by the type of adenomyosis into the focal or diffuse subgroup and by the localization of adenomyosis into the anterior wall or the posterior wall subgroup. Of the 504 patients who had sufficient data regarding the type and localization, 29.2% (147) had posterior wall—diffuse type, 21.2% (107) had posterior wall—focal type, 19.2% (97) had posterior wall—diffuse type, 18.3% (92) had anterior and posterior wall—diffuse type, 7.9% (40) had anterior wall—focal type, and 3.0% (15) had anterior and posterior wall—focal type. The pregnancy rates of these subgroups were >40% (range: 41.2%-46.7%). The miscarriage rate (41.5%) of the anterior and posterior wall—diffuse type subgroup was higher than in the other subgroups (23.5%-35.4%), but not to a significant degree (Table 4).

In order to analyze whether or not different types of adenomyosis influence female fertility differently, the patients were divided into two groups according to their type of adenomyosis: 162 patients had the focal type (adenomyoma) and 336 had the diffuse type. The pregnancy and miscarriage rates were 43.2% (70/162) and 24.7% (19/77) in the women with the focal type, respectively, and 42.9% (144/336) and 33.1% (54/163) in the women with the diffuse type, respectively. In the focal type, the pregnancy rate (no treatment: 43.0%; medication: 48.0%; operation: 39.1%) was not affected by pretreatment for adenomyosis; however, the miscarriage rate was lower in the patients who had undergone surgery (0%) than in those who received no treatment (29.1%) or medication (15.4%). In the diffuse type, the pregnancy rate (no treatment: 43.8%; medication: 42.9%; operation: 39.3%) and miscarriage rate (no treatment: 32.4%; medication: 37.0%; operation: 32.3%) were not affected by pretreatment for adenomyosis (Figure 1).

TABLE 4 Impact of the position and type of adenomyosis on the clinical outcomes of infertility treatment

Position and type of adenomyosis	Number of patients (n=504) N (%)	Pregnancy (N, %)	Miscarriage (N, %)
Anterior wall – focal	40 (7.9)	17 (42.5)	5 (26.7)
Anterior wall—diffuse	97 (19.2)	40 (41.2)	17 (35.4)
Posterior wall—focal	107 (21.2)	46 (43.0)	12 (23.5)
Posterior wall—diffuse	147 (29.2)	64 (43.5)	20 (27.0)
Anterior and posterior wall—focal	15 (3.0)	7 (46.7)	2 (25.0)
Anterior and posterior wall—diffuse	92 (18.3)	40 (43.5)	17 (41.5)
Anterior wall—focal, posterior wall—diffuse	3 (0.6)	0 (0.0)	–
Anterior wall—diffuse, posterior wall—focal	3 (0.6)	2 (66.7)	0 (0.0)

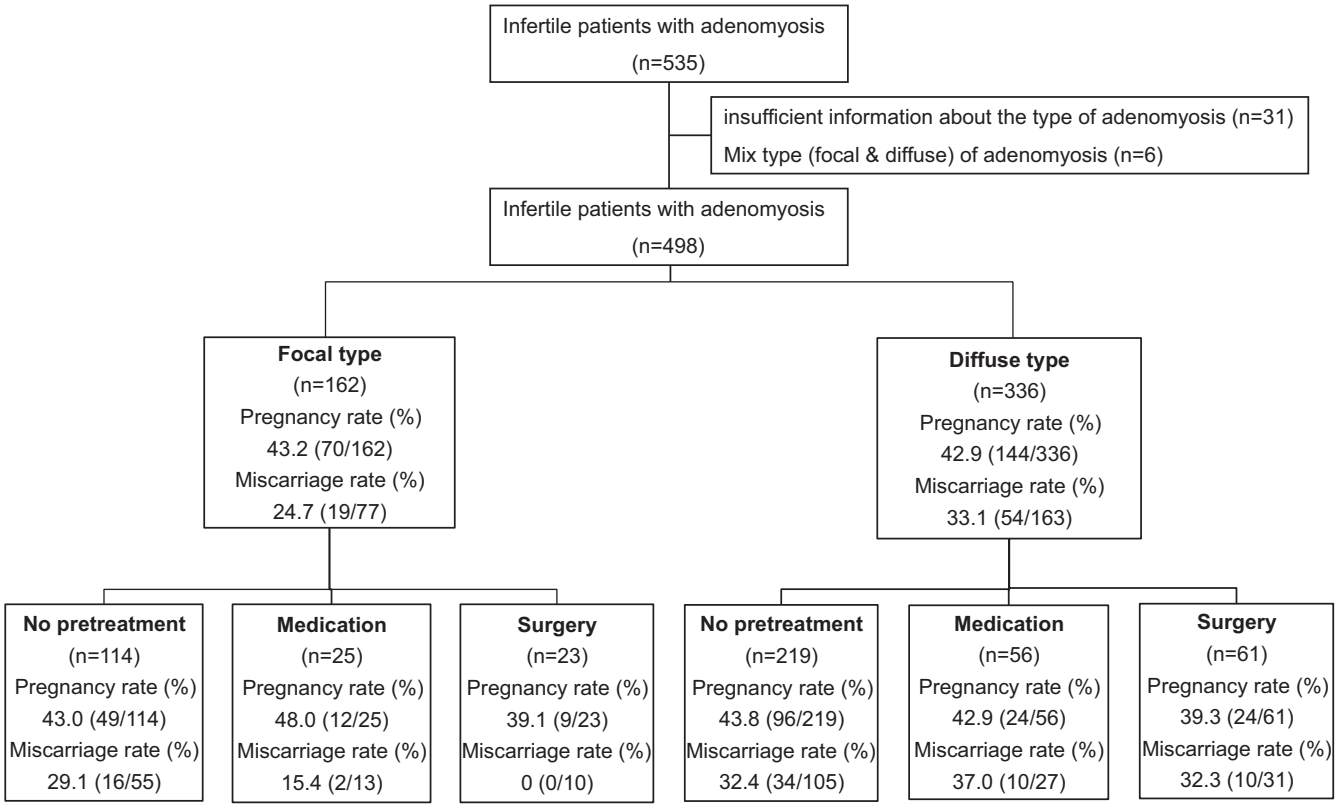

FIGURE 1 Flow diagram and the clinical outcomes of infertility treatment

4 | DISCUSSION

The present study is the first to conduct a large-scale, nationwide survey on the relationship between adenomyosis and infertility treatment. This study found that most Japanese facilities do not have a strategy for managing infertile women with adenomyosis, suggesting that a standard management policy has not been established. The association of adenomyosis with female fertility varies widely among individuals because the condition of the disease varies in size, type, localization, and severity. The presence of a concomitant pathology, including leiomyoma (35%-55%) and endometriosis (6%-20%), might drastically influence the fertility of women with adenomyosis.[5,22-24] As a high prevalence of endometriosis in women with adenomyosis was observed in the majority of the articles that reported on adenomyosis and fertility, the actual impact of the disease on female fertility is difficult to determine. Therefore, women with endometriosis and leiomyoma were excluded from this study.

A systematic review and meta-analysis showed that women with adenomyosis had a significantly lower clinical pregnancy rate (relative risk [RR]: 0.72; 95% confidence interval [CI]: 0.55-0.95) and had a

twofold increased risk of miscarriage (RR: 2.12; 95% CI: 1.20-3.75) than those without adenomyosis.[25] These findings suggest that, compared with the reproductive performance of women without adenomyosis, women with adenomyosis might have worse fertility. A number of potential biological mechanisms could underlie this effect, including the destruction of the normal myometrial architecture and function,[26] disturbed uterine peristalsis and sperm transport,[27,28] local hyperestrogenism,[29,30] abnormal inflammatory response,[31-33] increased presence of free radicals,[34,35] and hyper vascularization,[36,37] all of which have been reported in women with adenomyosis. However, many reports have noted no significant difference in the in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) outcome between women with and without adenomyosis.[12,14] A retrospective study of an oocyte donation program showed that the implantation and pregnancy rates were not affected by adenomyosis; furthermore, the endometrial gene expression profile that is involved in the implantation process and the endometrial receptivity of women with adenomyosis did not differ markedly from those of the controls.[13] However, these studies used varying criteria for the diagnosis of adenomyosis and the majority did not quantify the severity. The heterogeneity among the selected studies was also high due to the age of the participants, duration of infertility, coexistence of endometriosis and leiomyoma, protocol of IVF/ICSI, number and stage of transferred embryos, and number of IVF/ICSI cycles that was carried out. Therefore, exploring or studying the correlation between adenomyosis and fertility problems is difficult.

The present results show that the pregnancy rate from infertility treatment in women with adenomyosis is about 40%. The impact of adenomyosis on female fertility is unclear because the pregnancy rate could not be compared with control participants (those without adenomyosis) in this survey. However, this study's results are consistent with those of previous reports that showed the pregnancy rates (40%-50%) in women with adenomyosis,[25,38] suggesting that a considerable pregnancy rate would be expected in infertile women with adenomyosis. In addition, not only ART but also the usual infertility treatments without ART showed almost the same pregnancy rate (non-ART: 37.5%; ART: 44.4%). The present results suggest that ART might not necessarily be required for the first-step management of infertile women with adenomyosis.

The association of adenomyosis with an increased risk of miscarriage also has been suggested. The miscarriage rates in this survey were about 30% and no significant correlation was observed between the rates and pretreatment and size and type of adenomyosis. However, almost the same miscarriage rates in this study also were reported in several other studies. A miscarriage rate was observed in 31.8% (21/66) of the pregnancies in women with adenomyosis and in 12.5% (29/224) in those without adenomyosis,[10] while also in 32.8% (43/131) of women with adenomyosis and in 16.3% of the (24/147) controls.[13] These reports showed that the miscarriage rates were higher in women with adenomyosis than in those without adenomyosis. However, the factors that contribute to adenomyosis-related miscarriage could not be adequately assessed. In this regard, alterations in the inner myometrium of women with adenomyosis might result in defective remodeling of the spiral arteries during the decidualization process.[39] Further studies are required to properly evaluate the relationship between adenomyosis and pregnancy outcomes.

It is not known whether or not an improvement in reproductive performance can be achieved after the use of medical and/or surgical management. Case reports and small series studies have reported successful pregnancies after long-term GnRH agonist treatment.[40-42] However, there has been no large-scale study that has evaluated the efficacy of GnRH agonists before fertility treatment in women with adenomyosis. Of the 85 patients who had received medication before infertility treatment, 67 had received GnRH agonists in this survey. The pregnancy rate (43.5%) and miscarriage rate (31.7%) were not markedly different from the no-pretreatment group (41.3% and 30.3%, respectively). There were no data to suggest that medication as a pretreatment for adenomyosis increased the pregnancy rate in infertile women.

Although conservative surgery has not become the standard treatment for adenomyosis, successful pregnancies after conservative surgery in women with adenomyosis have been reported. The advantages of removing the affected area must be balanced against the disadvantages of leaving a possibly defective uterine wall. Therefore, there is a recognized difficulty in establishing the optimum conservative surgical technique for adenomyosis and several proposals, 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), have been reported.[19,43-45] In these reports, the successful pregnancy rates following infertility treatment ranged from 25.0% to 61.5% and the miscarriage rates ranged from 11.1% to 25.0%.[16,18,19,43-45] In the present study, of the 89 patients who underwent conservative surgery (open: 65 patients; laparoscopic: 24 patients), 41.6% (37) achieved pregnancy following infertility treatment. The pregnancy rate (41.6%) and miscarriage rate (26.1%) were not markedly different from the no-pretreatment group (41.3% and 30.3%, respectively). As the surgical techniques differed by facility, it is difficult to analyze the association between the reproductive outcome and each surgical technique. However, there were no data to suggest that conservative surgery as a pretreatment for adenomyosis increased the pregnancy rate in infertile women.

To the authors' knowledge, there are no data that assess the relationship between the size of adenomyosis and female fertility. A large adenomyosis probably can cause deformity of the uterine cavity and might impair implantation via the biological mechanisms described above. A recent report found a relationship between the uterine wall thickness (>15 mm) and the miscarriage rate in women with diffuse-type adenomyosis.[46] However, the size of adenomyosis was evaluated by the major axis of the focus, as a simple and objective indication for both types (focal and diffuse) in this survey. There was no significant relationship between the size of adenomyosis and the pregnancy rate. The miscarriage rate also did not show any notable association with the size of adenomyosis.

Previous reports have shown that adenomyosis develops more often in the posterior wall than in the anterior wall,[23,47] which is

consistent with this study's finding that the prevalence of the posterior wall—diffuse type (29.2%) and posterior wall—focal (21.2%) type were comparatively higher than that of the other patterns. Previous reports also have shown that diffuse-type adenomyosis is more common than focal-type adenomyosis: for example, diffuse type (81.7%) and focal type (18.3%)[4] and diffuse type (66.7%) and focal type (33.3%).[48] In the present survey, 66.7% (336) of the patients had diffuse-type adenomyosis (posterior wall—diffuse type: 147; anterior wall—diffuse type: 97; anterior and posterior wall—diffuse type: 92).

A recent report noted a higher clinical pregnancy rate in the focal type than in the diffuse type in women with adenomyosis who were undergoing IVF.[38] Furthermore, the immune balance between the regulatory T cells and the helper T cells in the uteri of women with diffuse adenomyosis was different from those of women with focal-type adenomyosis.[49] In order to analyze whether different types of adenomyosis influence female fertility differently, the women were subdivided into groups of those with the diffuse type and those with the focal type. Almost the same pregnancy rates were observed between those with focal adenomyosis (43.2%) and those with diffuse adenomyosis (42.9%). The miscarriage rate in those with diffuse adenomyosis (33.1%) was higher than that in those with focal adenomyosis (24.7%), but not to a significant degree. It was unable to be proven that the type of adenomyosis influences female fertility.

Also analyzed was the influence of medication and conservative surgery before infertility treatment on female fertility for both types of adenomyosis. Medication and conservative surgery did not improve the pregnancy rate in either type of adenomyosis, but no miscarriage was observed after conservative surgery in women with a focal adenomyosis. However, further studies are necessary in order to confirm whether conservative surgery and medication improve female fertility and whether the type of adenomyosis influences female fertility.

The present study is the largest survey to analyze the reproductive outcomes of infertile women with adenomyosis. A recent meta-analysis found that adenomyosis appears to negatively influence the IVF/ICSI outcome, owing to a reduced likelihood of clinical pregnancy and implantation and an increased risk of early pregnancy loss.[25] However, a high prevalence of endometriosis in women with adenomyosis was observed in the majority of these articles that reported on adenomyosis and fertility. Therefore, studies need to discriminate between women with adenomyosis only and those with endometriosis in addition to adenomyosis. Women with coexisting endometriosis and leiomyoma were excluded from the present survey in order to improve the understanding of the association between adenomyosis and infertility. It was found that the pregnancy rate with infertility treatment for infertile women with adenomyosis was about 40% and the miscarriage rate was about 30%. Almost the same pregnancy rates with infertility treatment were observed between the ART and non-ART subgroups, suggesting that ART might not necessarily be required for the first-step management of infertile women with adenomyosis. Neither the size nor the type of adenomyosis showed any association with the reproductive outcome. In addition, there were no data to suggest that medication or surgery as a pretreatment for adenomyosis improved the reproductive outcome. The data from this survey were not sufficient to analyze the actual relationship between adenomyosis and fertility because the response rate of this survey was low (16.5%; 190/1149 facilities). A prospective and well-conducted randomized study is required to evaluate the true effect of adenomyosis on fertility outcomes.

ACKNOWLEDGEMENTS

This survey was fully supported by JSOG. We thank the 190 facilities for responding to the questionnaires in this survey.

DISCLOSURES

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

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How to cite this article: Tamura H, Kishi H, Kitade M, et al. Clinical outcomes of infertility treatment for women with adenomyosis in Japan. *Reprod Med Biol*. 2017;16:276-282. https://doi.org/10.1002/rmb2.12036