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# A relationship between magnetic resonance imaging-based subtype classification and adenomyosis-associated infertility and obstetric complications

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## Abstract

***Objectives:*** *Patients with adenomyosis may present with a variety of clinical symptoms, including heavy menstrual bleeding, pelvic pain, and infertility. Magnetic resonance imaging (MRI) is an accurate and objective tool for the diagnosis of adenomyosis. MRI can classify adenomyosis according to disease subtypes, such as diffuse or focal, or intrinsic or extrinsic. The aim of this review is to provide current up-to-date information on the association between subtype classifications of adenomyosis and the severity of infertility and obstetric complications.*

***Methods:*** *Each keyword alone or in combination was used to search by applying the filters of the title and the publication years between January 2000 and December 2019.*

***Results:*** *There are many reports that the presence of adenomyosis worsens the clinical outcome after spontaneous pregnancy and in vitro fertilization (IVF)-embryo transfer (ET). Several researchers have examined the relationship between unique imaging criteria and disease severity. Many researchers have attempted subtype classification of adenomyosis by MRI. At least intrinsic and extrinsic adenomyosis have different etiologies and clinical manifestations. Intrinsic adenomyosis can cause miscarriage and future obstetric complications such as hypertensive disorder of pregnancy and preterm birth, while extrinsic adenomyosis may be associated with infertility.*

***Conclusion:*** *In conclusion, MRI-based subtype classification may be associated with infertility and obstetric complications in women with adenomyosis. A reporting system using subtype classification should be considered to discuss the relationship between adenomyosis and infertility and obstetric complications.*

**Keywords:** *adenomyosis; subtype; magnetic resonance image; infertility; obstetric complications.*

## Introduction

Adenomyosis is a benign uterine disorder characterized by the presence of endometrial glands and stroma within the myometrium [1,2]. This disorder is mostly diagnosed in 40s women in their reproductive age [3,4]. Adenomyosis has a negative impact on patients' quality of life and causes abnormal uterine bleeding, pelvic pain (dysmenorrhea), feeling of pelvic mass, infertility and obstetric complications; however, a third of adenomyosis cases can be asymptomatic [1,2,5-9]. Today, advances in diagnostic imaging techniques of adenomyosis have emerged including the use of dynamic, functional imaging with transvaginal ultrasonography (TVS) and magnetic resonance imaging (MRI) [1,8,10]. The prevalence has been reported to be in the range of 1-70% [1,8]. The true prevalence is still unknown because different imaging criteria are used [1,8]. In symptomatic women, adenomyosis is frequent and exists in about 40% of cases [11]. There has been some research on the association between the progression of adenomyosis and severity of baseline symptoms such as bleeding and pain [8,12]. Aleksandrovych et al. reported that the severity of abnormal uterine bleeding is thought to be related to the depth of endometrial penetration into the myometrium and that dysmenorrhea appears to be correlated with the number of endometrial glands in adenomyosis lesions [8]. However, the association between the image classification of adenomyosis and the severity of infertility and obstetric complications is not well known. Possible factors may include adenomyosis itself, the location and size of the lesions, complicated endometriosis, and adhesions around the uterus. The aim of this review is to provide current up-to-date information about what imaging parameters of adenomyosis correlate with the severity of infertility and obstetric complications. To this end, we summarize the latest information on diagnostic imaging classification, etiology underlying different phenotypes, and medical and surgical treatment for adenomyosis-related infertility.

| Key words | | No. of refs. | No. of eligible articles |
|---|---|---|---|
| **adenomyosis** | | | |
| | magnetic resonance imaging | 358 | |
| | diagnosis | 332 | |
| | classification | 23 | 19 |
| | infertility | 5 | 5 |
| | ultrasonography | 436 | |
| | diagnosis | 417 | |
| | classification | 37 | 30 |
| | infertility | 5 | 5 |
| | etiology | 792 | |
| | pathogenesis | 753 | |
| | infertility | 129 | 68 |
| | fertility outcome | 20 | 17 |
| | obstetric complications | 15 | 14 |
| | fertility outcome | 3 | 3 |

**Table 1.** The number of articles hit by searching for each keyword alone or in combination

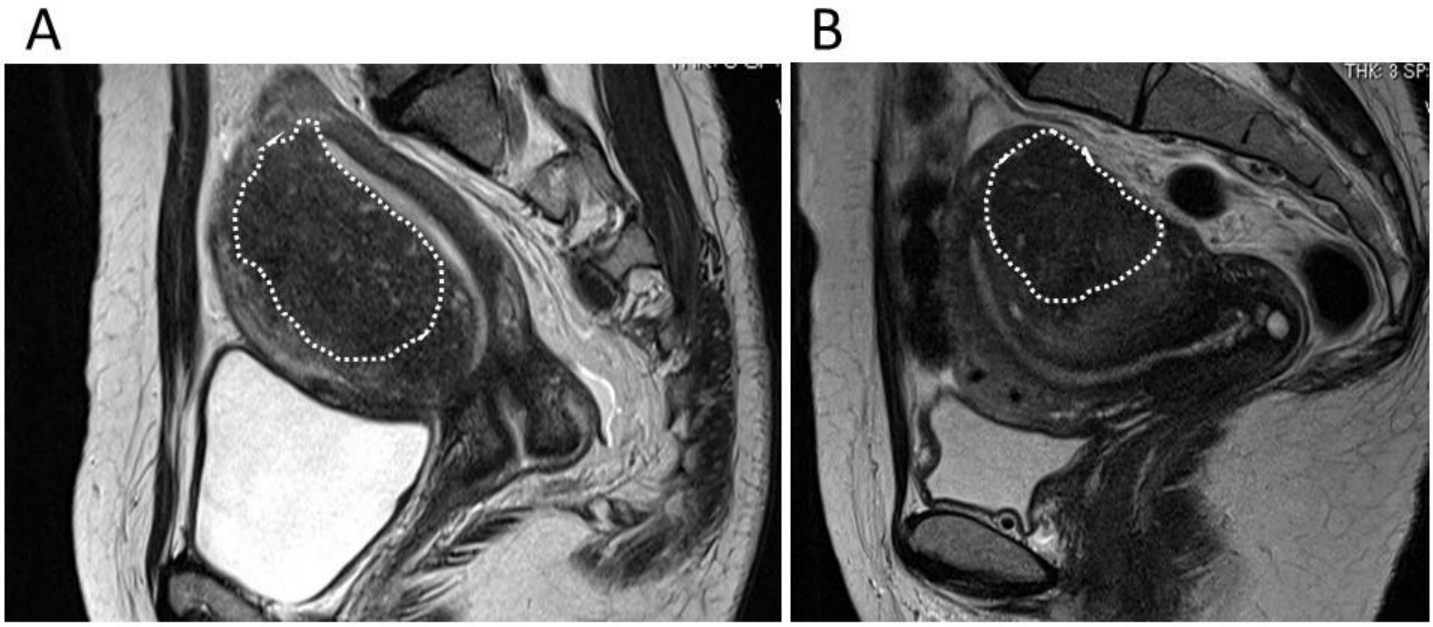


**Figure 1.** Typical example of subtype classification of adenomyosis

A, Intrinsic adenomyosis. Adenomyosis lesions are found on the anterior wall of the uterus. The lesion continuously invades the myometrial layer from the endometrium, does not reach the serosa of the uterus, and a normal outer myometrium is observed. B, Extrinsic adenomyosis. The JZ around the endometrium is normal. Adenomyosis is located from the posterior wall of the uterine myometrium to the serosa side, with normal inner myometrium.

## Data collection methods

### Literature search

A computerized literature search was conducted to identify relevant studies reported in the English language. We collected a comprehensive literature search from PubMed and Embase database between January 2000 and December 2019, combining the keywords "adenomyosis" combined with “diagnosis”, “ultrasonography”, “magnetic resonance imaging”, “infertility”, “fertility outcome”, “obstetric complications”, “etiology”, “pathogenesis”, and “classification”. A variety of combinations of these terms were used, depending on which database was searched (Table 1). Furthermore, the references of each article were searched to identify potentially relevant studies. Publications of original studies, review papers and some guidelines were included, while those documenting opinions, points of view or anecdotes were excluded.

Each keyword alone or in combination was used to search by applying the filters of the title and the publication years between 2000 and 2019. This table shows the number of articles searched by keywords and the number of eligible articles among them and that, for example, the number of articles hit by searching for keywords for ‘adenomyosis’ AND ‘magnetic resonance imaging’ AND ‘diagnosis’ AND ‘classification’ is 23. Among the 23 articles, nineteen articles were eligible.

## Results

### Diagnostic imaging classification of adenomyosis

Traditionally, adenomyosis was diagnosed based on the finding in specimens obtained from hysterectomy, but recent advances in high-resolution TVS and MRI have facilitated the diagnosis of adenomyosis [5,7,8,13,14]. First, imaging with TVS has often been used in the clinical setting for the diagnosis of adenomyosis. Two-dimensional (2D) -TVS imaging of adenomyosis is based on the presence of globular uterine configuration, asymmetrical myometrial thickening, irregular endometrial-myometrial junction (JZ), poor definition of the JZ, heterogeneous myometrial echotexture, subendometrial or myometrial cysts, myometrial anechoic lacunae, hypoechoic striation or islands in the myometrium, linear striations, parallel shadowing, and localized adenomyomas [7,15-17]. The most common TVS feature observed is asymmetrical myometrial thickening of the uterine walls with heterogeneous myometrium [17]. It is necessary to distinguish between diffuse and focal adenomyosis, identify the localization of individual lesions, and confirm the JZ thickness for classification by imaging. It is relatively easy to diagnose the spread of adenomyosis lesions using TVS. Pinzauti et al. reported that one of the 3D-TVS imaging-based diagnostic criteria for adenomyosis is the JZ thickness ≥8 mm [17]. Most of the women with sonographic features of diffuse adenomyosis were symptomatic, had dysmenorrhea in 80%, and had more heavy bleeding than women without these clinical symptoms (18.9% vs 2.9%) [17].

We next describe the recent advances in diagnostic approaches on MRI to adenomyosis. Many elegant reviews have been reported [6,7,10,18,19]. MRI is an accurate and objective tool for the diagnosis of adenomyosis. The established MRI findings are the uterine JZ thickness exceeding 12 mm and high-signal intensity myometrial foci on T2- or T1-weighted images [18,20]. Adenomyosis is suspected if the JZ thickness is 8-12 mm. Adenomyosis is likely to be diagnosed as a diffuse or focal form, with a ratio of about 2: 1 [21]. Recent advances in MRI diagnosis have made it possible to understand which types of adenomyosis correlates with disease severity or specific clinical symptoms such as bleeding and pain [8]. Several researchers have examined the relationship between unique imaging criteria and disease severity: diffuse adenomyosis and intrinsic adenomyosis may correlate with abnormal uterine bleeding, while extrinsic adenomyosis and coexistence of deep infiltrating endometriosis (DIE) may be associated with painful menstruation [8,12,22]. In this paper, we mainly adopted the Kishi’s classification and categorized adenomyosis into ‘intrinsic’ and ‘extrinsic’ [12]. Figure 1A is a typical example of intrinsic adenomyosis, in which adenomyosis progresses from the lumen of the uterus toward the outer muscle layer of the anterior wall of the uterus. On the other hand, figure 1B shows a case of extrinsic adenomyosis, in which no abnormality is observed in JZ, but adenomyosis progresses from the uterine serosa side toward the inside of the uterus.

Diagnostic imaging of adenomyosis requires strict criteria and disease classification, but one of the major obstacles is the lack of precise criteria for predicting adenomyosis-associated infertility. There has been no evidence that asymptomatic adenomyosis patients do not cause infertility. For example, physicians sometimes encounter young women with asymptomatic adenomyosis during a work-up for infertility [3,10]. At this time, there has been no report on the diagnostic imaging criteria that can predict which adenomyosis patients are currently suffering from infertility or will become infertile. To assess the correlation between diagnostic imaging and symptom severity, clinical data should be obtained on the age of the patient, the severity of symptoms such as bleeding, pain and infertility, duration of symptoms, complication of endometriosis, and radiological features of the lesions. To harmonize the classification of adenomyosis with the severity of the disease, diagnostic imaging should be registered according to a unified and shared reporting system [19].

### The possible origin of adenomyosis.

Understanding the etiology of adenomyosis can help elucidate the cause of infertility. There are some similarities between adenomyosis and endometriosis, which are pathological distinguished by location of ectopic endometrium [6,7,8,23]. Although the exact mechanisms underlying the origin, evolution and progression of adenomyosis remain unknown, three main theories have been proposed to explain the origin of adenomyosis [2,6,7]. First, the most common is the theory of invagination (benign invasion) of the endometrial basalis into the myometrium (the origin of intrinsic adenomyosis, so-called classic adenomyosis) (Figure 1A) [6]. This theory supports the hypothesis that adenomyosis causes alterations in the JZ and inner myometrial layer [7]. The second theory is that endometriosis adheres to the serosa of the uterus, infiltrates into the outer myometrial layer and promotes the formation of adenomyosis lesions (the origin of extrinsic adenomyosis) (Figure 1B). This hypothesis is supported by the fact that extrinsic adenomyosis often coexists with endometriosis [12]. Adenomyosis and endometriosis have traditionally been considered as separate entities with different etiologies [13,24],

but some researchers believe that extrinsic adenomyosis results from endometriosis [5]. Further, several researchers have found that endometriosis itself can cause functional and structural changes in JZ, even in the absence of an adenomyosis lesion [23,25]. Therefore, the presence of endometriosis may be involved in the development of adenomyosis. The third theory is that adenomyosis may have arisen from de novo metaplasia of the embryological Müllerian-duct remnants (so-called metaplasia theory) [6,7]. Adenomyosis can appear as a 'diffuse' form when either intrinsic adenomyosis progresses outward or extrinsic adenomyosis progresses inward and ill-defined lesions are often dispersed within the myometrium [26]. Therefore, it is difficult to determine whether the origin of diffuse adenomyosis is intrinsic or extrinsic. There is no doubt that endometrial cell infiltration into the muscle layer is the first step in the development of intrinsic and extrinsic adenomyosis [27].

In addition, this article provides the genetic and molecular changes that characterize the development of adenomyosis. Emerging studies have demonstrated that sex steroid hormone receptors, inflammatory molecules, extracellular matrix enzymes, decidualization-related genes, apoptosis-suppressing genes and growth factors, epithelial-mesenchymal transition and neuroangiogenic factors are the key mediators [13,28]. The expression of some decidualization-related genes, including homeobox A10 (HOXA10) [29], forkhead box O1 (FOXO1A) [30], and Krüppel-like factor 12 (KLF12) [31], can be downregulated in adenomyosis. These genes are observed to be downregulated in endometriosis [32-34]. Recent study demonstrated that transforming growth factor-beta (TGF-β) is a multifunctional growth factor that plays important roles in the regulation of fibrogenesis in both endometriosis [35] and extrinsic adenomyosis [28,36]. Conversely, intrinsic adenomyosis causes fibrosis through a TGF-β signaling-independent mechanism [36]. The mechanism of fibrosis in extrinsic adenomyosis may be similar to endometriosis, but differs from intrinsic adenomyosis [12,24]. The fact that extrinsic adenomyosis and endometriosis are pathophysiologically similar suggests that extrinsic adenomyosis is more associated with infertility than intrinsic adenomyosis. Advances in molecular biology have led to the idea that the development of adenomyosis may be triggered by a combination of multiple processes, rather than a single mechanism [6]. To date, it remains unclear whether adenomyosis and endometriosis are different manifestations of the same syndrome or are two distinct entities, but the presence of endometriosis may be associated with the development of extrinsic adenomyosis.

**A link between the subtypes of adenomyosis and infertility severity**

Reproductive disorders, including endometriosis, adenomyosis, uterine fibroids and polycystic ovary syndrome, can be associated with unexplained infertility [37]. Some data on the effectiveness of medical and surgical treatment options for adenomyosis is available to investigate the prevalence of infertility [3,15,38-40]. Until recently, there was considerable agreement that adenomyosis did not adversely affect fertility [41]. The recent increase in the incidence of adenomyosis in infertile women is due to the late marriage and childbirth of Japanese women, who face social infertility [41]. The success rates of implantation, spontaneous pregnancy, clinical pregnancy (per cycle or per embryo transfer), and live birth were lower in modern women with adenomyosis than in those without [38,42]. This disorder is also known to negatively affect the clinical outcome of IVF [43]. Animal experiments with baboons have been reported to support a causal relationship between adenomyosis and infertility [44].

It is important to determine whether infertility is directly affected by adenomyosis itself, or indirectly caused by known various complications of adenomyosis, such as endometriosis and adhesions around the uterus. Endometriosis-related diseases, such as DIE and adhesions, superficial endometrial implants and ovarian endometrioma, are significant risk factors for infertility [45]. Recent review article showed that in adenomyosis patients with DIE, surgical treatment for DIE can improve pelvic pain [41], while surgery for rectovaginal and colorectal endometriosis has been reported to have a marginal effect on improving fertility [39,46]. Treatment of deep endometriosis alone does not improve infertility in a case of adenomyosis complicated with deep endometriosis, suggesting that adenomyosis itself can cause infertility, decrease the rate of live birth and increase the risk of obstetric complications [10,25,46]. These data suggest that adenomyosis itself has a more negative impact on fertility compared to DIE.

Furthermore, the extent, spread, or severity of the disease, such as diffuse adenomyosis or complication of deep endometriosis, does not always correlate with the frequency of infertility [15]. In addition, there is no scientific evidence showing that diffuse adenomyosis is more prone to infertility than focal adenomyosis [15]. Despite a causal link between adenomyosis and infertility, a consensus on the link between infertility and the severity of adenomyosis at surgery has not emerged [15]. The therapeutic decision should be based on a comprehensive evaluation that includes patient age, married or unmarried, number of children, complications including pain, bleeding and infertility, pre-existing pregnancy complications, imaging findings, as well as women's wishes [45].

Given the above evidence, the purpose of this chapter is to investigate which subtypes of adenomyosis are more positively associated with reduced fertility or infertility. Some researchers believe that adenomyosis is composed of multiple subtypes with distinct images and clinical features. [12,19,36,47]. First, as shown in Figure 1, adenomyosis has been classified into 'intrinsic' and 'extrinsic' based on imaging diagnosis [48]. Intrinsic and extrinsic adenomyosis may be associated with multi-gravidity/multiparity and infertility, respectively (12).

As mentioned in the previous chapter 'The possible origin of adenomyosis', intrinsic adenomyosis can cause structural and functional changes in the JZ and inner myometrial layer, leading to reduced fertility or infertility [25]. In the assessment of uterine function, uterine peristalsis or contraction has been evaluated at the sagittal and coronal planes of cine MRI [49]. Structural abnormalities caused by thickening of the JZ and inner myometrial layer induce abnormal uterine peristalsis, leading to uterine bleeding, implantation failure and miscarriage [10]. Thus, intrinsic adenomyosis may be associated with early pregnancy loss and recurrent miscarriage rather than causing infertility.

On the other hand, extrinsic adenomyosis predominantly occurs in the posterior uterine hemisphere with posterior cul-de-sac obliteration, posterior cul-de-sac endometriosis, ovarian endometrioma and deep infiltrating endometriosis (DIE), causing severe cramping pain and infertility [12,45,46,50]. This type of

adenomyosis increases the frequency of assisted reproductive technologies (ART) [51]. Thus, extrinsic adenomyosis, like endometriosis, may be associated with unexplained infertility.

**An association between the subtypes of adenomyosis and obstetric complications**

The purpose of this chapter is to identify possible links between adenomyosis subtypes and pregnancy complications. Epidemiological data suggest that women with adenomyosis are at increased risk for many obstetric complications, including preterm birth, preterm premature rupture of membranes, placenta previa, placenta abruption, hypertensive disorder of pregnancy (HDP), postpartum hemorrhage due to uterine atony, fetal malpresentation, uterine rupture, bowel perforation, spontaneous hemoperitoneum, ectopic pregnancy, and cesarean section [3,4,8,37,38,40-43,52-56]. Uterine rupture and preterm birth were observed in 6.8% and 4.5% of diffuse adenomyosis patients and 0% and 10.9% of focal adenomyosis patients, respectively [54]. With a few exceptions [39], there are many papers showing that adenomyosis increases the risk of obstetric complications.

We discuss why adenomyosis is associated with obstetric complications. Functional and structural alterations in the endometrium, JZ and inner myometrial layer, which are more likely to occur in women with intrinsic adenomyosis, result in poor trophoblast invasion and inadequate myometrial spiral arteries remodeling, causing dysregulated decidualization, persistent high vascular resistance and increased risk of defective deep placentation [4,23]. Obstetric complications such as HDP have been linked to defective remodeling of myometrial spiral arteries [43]. Furthermore, functional defects in the inner myometrial layer in adenomyosis, such as impaired peristalsis and hyperperistaltic of the uterus, can adversely affect the course of pregnancy, including preterm birth [14,37,43,53,57,58,59]. Thus, intrinsic adenomyosis is likely to cause future obstetric complications, including HDP and premature delivery.

On the other hand, extrinsic adenomyosis, like endometriosis, is often associated with infertility, as described in the previous chapter. Therefore, ART is likely to increase in extrinsic adenomyosis. It is unclear whether the adverse effect is due to extrinsic adenomyosis itself or the effect of ART, because pregnant women after IVF are at increased risk for obstetric complications [51]. Recently, Harada et al. reported that patients with adenomyosis have significantly increased obstetric complications, even after adjusting for the influence of ART outcomes [60].

Information about future obstetric complications before pregnancy is valuable for women with adenomyosis [43].

**Assisted reproductive techniques and conservative surgical treatment for adenomyosis-associated infertility**

We next investigate whether there is a difference in the effects of ART and conservative surgical treatment between intrinsic and extrinsic adenomyosis. Hysterectomy is a definitive solution for patients with symptomatic adenomyosis who do not wish to preserve fertility and their uterus [7,9]. Medical treatment, ART and conservative surgery can be offered to reproductive-aged women who desire future pregnancy [9,61]. The most commonly used medications are non-steroidal anti-inflammatory drugs (NSAIDs), progestogen and gonadotropin-releasing hormone (GnRH) agonists [9]. Hormonal therapy with progestogen and GnRH agonists is a frequently used treatment for abnormal uterine bleeding and pain symptoms [9]. This chapter summarizes the effects of conservative treatments, including IVF and fertility-sparing surgery, on reproductive outcome in women with adenomyosis-associated infertility, but does not address treatment option for pain and bleeding using hormonal therapy.

**IVF treatment**

Most of the papers target all patients with adenomyosis without classifying them into subtypes. A meta-analysis of published data revealed that women with adenomyosis have a 28% reduction in clinical pregnancy for IVF/ICSI compared to women without adenomyosis due to reduced likelihood of clinical pregnancy and increased risk of early pregnancy loss [62]. Also, a systematic review showed that adenomyosis had adverse effects on IVF outcomes [9]. Many case-control and cohort studies also revealed that adenomyosis caused a negative impact on IVF outcomes [5,14,22,38,43,45,63- 65]. Representative papers are shown below. The following morphological features are used to diagnose adenomyosis: asymmetrical myometrial thickening of the uterine walls, diffuse or focal subtype, poor definition of the endometrial-myometrial interface and myometrial heterogeneity. The greater the number of morphological features, the lower the clinical outcome of IVF-ET [22,63]. Mavrelos et al. investigated the pregnancy outcomes in 375 infertile women with adenomyosis after IVF-ET [63]. The clinical pregnancy rate significantly reduces in adenomyosis patients undergoing GnRH antagonist stimulation for IVF treatment compared to those without adenomyosis (23.6-29.2% vs. 42.6-44.6%) [63,65]. In infertile women undergoing IVF, 19 patients with adenomyosis had lower clinical (22.2% vs. 47.2%) and ongoing (11.1% vs. 45.9%) pregnancy rates compared to 256 women without adenomyosis, respectively [14]. Women with adenomyosis had significantly higher miscarriage rate compared with those without adenomyosis (50.0% vs. 2.8%) [14]. The prevalence of adenomyosis was significantly higher in the recurrent miscarriage group (38.2% vs. 22.3%) and the previous ART failure group (34.7% vs. 24.4%) compared to the control group [65]. Yan et al. conducted a cohort study collected from 10,268 patients with adenomyosis who underwent controlled ovarian hyperstimulation and IVF / ICSI to investigate live birth rates [64]. Women with adenomyosis have significantly lower delivery rate compared with those without ($p = 0.022$) [64]. Adenomyosis could have a negative impact on reproductive outcomes, including a detrimental effect on the clinical outcome of IVF, increasing miscarriage rates and decreasing pregnancy and birth rates.

There are few papers examining the therapeutic effect on infertility by classifying adenomyosis into intrinsic or extrinsic type, and focal or diffuse disease. The clinical outcome of IVF was significantly lower in adenomyosis externa or DIE than in the control group [45], suggesting that IVF treatment may be less effective in patients with extrinsic adenomyosis. At present, the lack of widespread use of diagnostic criteria using MRI and the small sample size makes it difficult to compare the subtype classification of adenomyosis and the efficacy of IVF treatment.

On the other hand, there is a small number of reports that adenomyosis does not affect the clinical outcome of IVF [55,66,67]. Costello et al. investigated the effect of adenomyosis on IVF/ICSI treatment outcome and showed that there was no difference in live birth rate per patient (cycle) between women

with adenomyosis and those without (29.7% vs. 26.1%; p=0.395; OR 1.45 with 95% CI 0.61-3.43) [67]. Benaglia et al. also reported that the presence of adenomyosis did not adversely affect implantation rate in women undergoing IVF/ICSI treatment [66]. The majority of the studies report a negative impact on IVF outcomes, but the quality of the evidence generated by these studies is low, due to inconsistency in the results.

**Fertility-sparing surgery**

Several studies include cases treated with IVF protocol alone without fertility-sparing surgery and those who underwent conservative surgery followed by IVF protocol. We review the impact of surgical treatment on reproductive outcomes in infertile women with adenomyosis. In a total of 102 adenomyosis women who had a desire for pregnancy, conservative surgery was beneficial, especially for women under the age of 39 who have experienced IVF treatment failure [48]. Conservative surgery is not only effective in relieving pain, but also in improving fertility, and about 50% of adenomyosis patients can expect a spontaneous pregnancy [50,61], indicating that surgical treatment increases the pooled spontaneous pregnancy rate [42]. Tskhay et al. reported that in a small case study, conservative surgery for severe adenomyosis is an excellent alternative to hysterectomy [68]. A retrospective cohort study and systematic review of the literature summarize that among the variety of treatment options, fertility-preserving surgery for severe adenomyosis was effective in controlling symptoms such as heavy menstrual bleeding and dysmenorrhea, and possibly in adenomyosis-associated infertility [1,52,54,55]. Surgical treatment options should be recommended if medical treatment, including IVF, is ineffective.

We examined the effects of conservative surgery in the combination with other treatment options. Younes and Tulandi reported that treatment with GnRH agonists increased spontaneous pregnancy rates in women with adenomyosis [42]. Furthermore, the combination of conservative surgery with GnRH agonist treatment appears to restore fertility in patients with adenomyosis [10]. Studies cited include case series and retrospective studies, but not prospective clinical trials [52].

Is there a significant difference in the effectiveness of conservative surgery in improving infertility in patients with diffuse and focal adenomyosis? Both patients with diffuse and focal adenomyosis have a miscarriage rate of more than 20%, twice as high as normal pregnant women, suggesting that the rate of abortion does not depend on the extent of adenomyotic lesions [54]. High frequency of preterm births may reduce live birth rates in patients with diffuse adenomyosis compared to focal adenomyosis (52.7% vs. 34.1%) [54]. This indicates that diffuse adenomyosis is associated with the reduced live birth rate. In addition, even focal adenomyosis adversely affects fertility and pregnancy outcomes for the following reasons: first, focal lesions structurally and functionally affect the JZ and inner myometrial layer; second, some of the focal adenomyosis, such as extrinsic adenomyosis, adversely affects fertility preservation; and finally, focal adenomyosis located in the outer myometrium (FAOM) is often associated with endometriosis, especially DIE [69]. Thus, surgical treatment of adenomyosis, whether diffuse or focal, may improve fertility [40].

Although conservative surgery may improve obstetric complications, women having surgery are at increased risk of post-operative complications. Uterine rupture and preterm birth after conservative surgery were observed in 6.8% and 4.5% of diffuse adenomyosis patients and 0% and 10.9% of focal adenomyosis patients, respectively [54]. The rate of uterine rupture during pregnancy after adenomyomectomy (6.0%) is much higher than the rates of complications after cesarean section (0.2%-0.7%) and myomectomy (2.4%) [1,2,70]. Taking into account the side effects, surgical treatment should be considered on a case-by-case basis in the following cases: patients with concurrent adenomyosis-related heavy menstrual bleeding and severe cramping pain, refractory patients with reduced fertility, such as diffuse adenomyosis, patients with focal adenomyoma who adversely affect fertility preservation, patients with a history of recurrent pregnancy loss or implantation failure, patients who are not eligible for long-term medical treatment, infertile patients younger than 35 years who have failed medical treatment, or infertile patients older than 40 years who have failed ART [1,2,52,54,61,68].

In summary, conservative surgery may improve fertility in patients with extrinsic adenomyosis even if it is a focal type. Since patients with intrinsic adenomyosis often have obstetric complications such as preterm birth, conservative surgery may improve obstetric complications in patients with diffuse type, but there are many postoperative complications. However, there is currently no strong evidence that adenomyosis subtypes influence the efficacy of ART and conservative surgery.

## Conclusion

Multiple case series and controlled studies have been reported on the relationship between adenomyosis and infertility and adverse pregnancy outcomes. In general, adenomyosis itself adversely affects reproductive outcome, including successful implantation, spontaneous pregnancy, and clinical pregnancy [4,38,42,43,52,54-56]. This disorder has also a negative impact on pregnancy complications, including fetal malpresentation, placenta previa, preterm birth, placenta abruption, postpartum hemorrhage, and cesarean section [3,4,8,38,40-43,52-56]. Adenomyosis is also known to negatively affect the clinical outcome of IVF [5,14,43,52,63,64]. Thus, women with adenomyosis are at increased risk of infertility and future obstetric complications. Therefore, we investigated whether the severity of infertility and obstetric complications could be predicted by subtype classification and spread of disease, not by overall adenomyosis.

This review suggests that adenomyosis is a heterogeneous disease of different etiology, and the frequency of infertility and perinatal complications may differ by subtype. Intrinsic adenomyosis should be noted for obstetric complications rather than infertility. On the other hand, extrinsic adenomyosis may have more infertility because its etiology is similar to endometriosis. However, it was not possible to evaluate whether adenomyosis subtypes influence the therapeutic effects of ART and conservative surgery due to insufficient evidence.

First, it is considered that intrinsic adenomyosis causes miscarriage due to implantation failure, and premature birth is complicated when adenomyosis spreads diffusely in the muscle layer. The rate of miscarriage is not statistically different between diffuse and focal adenomyosis [15,22,54], suggesting that both diseases reduce fertility as well. This may be because even focal

lesions structurally and functionally affect the JZ and inner myometrial layer. The frequency of overall obstetric complications does not seem to differ significantly between diffuse and focal adenomyosis [4,43,54-56], but premature birth is more common in diffuse adenomyosis than in focal adenomyosis [22,54]. Diffuse adenomyosis may lead to premature labor due to poor extension of the myometrium during pregnancy.

Second, extrinsic adenomyosis may be associated with infertility because of its etiology similar to endometriosis. In particular, DIE associated with extrinsic adenomyosis also increases the frequency of infertility. Extrinsic adenomyosis itself may be responsible for infertility because surgery of DIE alone does not improve fertility.

Third, the advances in diagnostic imaging of MRI have made it possible to establish a new subtype classification of adenomyosis [2,6,7,12,19]. However, the subtype classification of adenomyosis is not widespread. The MRI-based reporting system should be conveniently used in clinical setting, use standardized terminology, and convey actionable information [71]. To assess the association between adenomyosis and infertility or perinatal complications, it is essential to establish subtype classification prior to pregnancy.

Finally, several important issues have been noted, including the paucity of high quality research articles, different definitions of infertility, diagnosis using either TVS or MRI, and the use of different diagnostic criteria. There are only insufficient papers to evaluate the association between imaging classification of adenomyosis based on unified diagnostic criteria and the effect of conservative surgical treatment. Further clinical study is needed to determine whether a subtype classification system can predict the risk of infertility and future obstetric complications.

In conclusion, the subtype classification of adenomyosis, including intrinsic or extrinsic, diffuse or focal, or complications of endometriosis, may predict the severity of infertility and future obstetric complications. Since endogenous adenomyosis can cause miscarriage and obstetric complications, and extrinsic adenomyosis can cause infertility, we believe that it is necessary to perform MRI-based subtype classification before starting treatment.


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### Author's contribution

Shogo Imanaka, Sachiyo Maruyama, Mai Kimura, Mika Nagayasu, and Sho Matsubara performed the literature search and collected data using the Web database. Mai Kimura and Hiroshi Kobayashi made substantial contribution to conception of the study. Sho Matsubara contributed to the study design and interpretation of included research studies. The final version of the manuscript has been read and approved by all authors.

### Competing interests

The authors declared no potential conflicts of interest with respect to the research, authorship and publication of this article.

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