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Review Article

Conservative surgical treatment of adenomyosis to improve fertility: Controversial values, indications, complications, and pregnancy outcomes[☆]



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ABSTRACT

Uterine adenomyosis was first reported in the 19th century and early 20th century; von Rokitsky described it in 1860. Since then, the general clinical, pathological, and radiologic findings and potentially useful management methods have been reviewed in many studies. Some authors commented that conservative surgical treatment is impracticable as it is not possible to isolate the adenomyotic tissue adequately; therefore, the authors suggested that hysterectomy is the only rational and complete procedure. There is more evidence supporting the advantages of conservative uterine-sparing surgery in providing not only more effective symptom relief, but also longer durable symptom control for symptomatic women with uterine adenomyosis, because the main problem secondary to uterine adenomyosis, dysmenorrhea, can be improved significantly, up to 80%. Menorrhagia was also improved in more than two-thirds of patients after type I uterine-sparing surgery, and half of the patients saw benefit in symptom control after type II conservative uterine-sparing surgery. In addition, there was no negative impact on reproductive performance after conservative uterine-sparing surgery, and in fact, reproductive performance seemed to be improved compared with that after medical treatment—not only was there a higher cumulative pregnancy rate, but also a higher cumulative final successful delivery rate. However, there is no doubt that the data supporting the above-mentioned benefits for symptomatic women with uterine adenomyosis after conservative uterine-sparing surgery are limited, suggesting that the benefit may be moderate. In fact, one of the main indications for surgery is temporary pain relief in women seeking spontaneous conception. However, the effect of surgery on pain is usually only temporarily satisfactory, and the risk of complications varies according to the type of lesion extirpated. In light of this, an extensive review of this topic addressing conservative surgical treatment for adenomyosis to improve fertility, including

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controversial values, indications, complications, and pregnancy outcomes, might be very important, and might help physicians in managing these patients in the future.

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Introduction

Karl Freiherr von Rokitansky [1], in 1860, reported the first pathologic description of adenomyosis—some fibrous tumors in the uterus that contain gland-like structures that resemble endometrial glands, and the tumors appear to have roots deep within the uterine muscle layers, so it is hard to distinguish the border of these tumors within the surrounding myometrial tissues [2]. Adenomyosis is known as “endometriosis (or endometrial glands) of the myometrium in the uterus”, and these ectopic endometrial tissues appear to induce hypertrophy and hyperplasia of the surrounding myometrium with resultant diffusely enlarged uterus [3].

Adenomyosis remains an enigmatic disease and a cause of abnormal uterine bleeding and dysmenorrhea, subsequently resulting in chronic pelvic pain and infertility [4]. Adenomyosis-associated morbidity has a significantly negative impact on women's quality of life, and contributes to long-term major health issues. Therefore, a better understanding of adenomyosis might allow less invasive but more accurate diagnostic tests and much more effective treatment. Although we recently reviewed medical treatment and uterine-sparing surgery for adenomyosis [5,6], we wanted to assess whether conservative surgical treatment for adenomyosis can improve fertility through understanding the disease in women undergoing conservative uterine-sparing surgery and by discussing the following issues: controversies, indications, complications, and pregnancy outcome.

Controversy

The need for hysterectomy to diagnose adenomyosis means that it is not easy to diagnose preoperatively. The specificity of a preoperative diagnosis of adenomyosis based on clinical findings is poor, ranging from 2% to 26% [7]. The clinical triad of uterine adenomyosis includes abnormal uterine bleeding (nearly 50%), secondary dysmenorrhea (nearly 30%) and an enlarged, tender uterus [4]. However, many cases of adenomyosis are asymptomatic, and it usually affects multiparous women over the age of 40 years [8]. Clinical diagnoses are suspected after an imaging study or after obtaining an accidental pathological finding when uterine surgery is performed for other indications, suggesting that many cases of adenomyosis go undetected, and this limits our understanding of the prevalence and clinical impact [7]. There have been several pathology-based studies published in which women with adenomyosis found at hysterectomy were often more parous than women in which it was not found [9].

There is a lack of consensus in the literature regarding the relationship between adenomyosis and its associated disease-related clinical problems, such as fertility. This might have resulted from the retrospective nature of the majority of studies and that they mainly included populations undergoing hysterectomy [10]. In addition, these studies used differing criteria for the diagnosis of adenomyosis, and the majority of them did not quantify the severity. The results of retrospective studies showed the absence of a relationship between adenomyosis and the clinical pregnancy rate. In the adenomyosis group, 99 of 206 women had clinical pregnancy, contributing to 48.1% of the clinical pregnancy rate [11].

Compared with the clinical pregnancy rate of 55.1% (383/695) among women without adenomyosis, there was no statistically significant difference between the women with and without adenomyosis [risk ratio (RR) 0.84, 95% confidence interval (CI) 0.67–1.06, $p = 0.220$] [11]. By contrast, prospective studies showed a significant difference in the clinical pregnancy rate between women with and without adenomyosis. Women with adenomyosis had a significantly lower clinical pregnancy rate (24/98, 24.5%) than women without adenomyosis (245/567, 43.2%), with an RR of 0.55 and a 95% CI ranging from 0.32 to 0.96 [11].

In addition, the use of different diagnostic tools also influenced the results of the studies. Diagnoses made by ultrasound showed absence of a relationship between adenomyosis and clinical pregnancy rate, but diagnoses made by magnetic resonance imaging (MRI) showed a strong association between adenomyosis and clinical pregnancy rate. Of 244 women with ultrasound-diagnosed adenomyosis, 109 finally had a clinical pregnancy (44.7%), relatively similar to the clinical pregnancy rate of 1095 women without adenomyosis (48.3%); there was no statistically significant difference between the two groups (RR 0.84, 95% CI 0.68–1.04). By contrast, diagnoses by MRI showed the significantly negative impact of adenomyosis on the clinical pregnancy rate (RR 0.40, 95% CI 0.25–0.64) [11], suggesting that different study designs contributed to uncertain and/or inconsistent results. Therefore, the potential effect of adenomyosis on fertility continues to be debated.

Furthermore, the presence of a concomitant pathology, for example, leiomyoma (35–55%), endometriosis (6–20%), endometrial polyps (2–3%), endometrial hyperplasia with/without atypia or neoplasms (> 10%), poor ovarian responders (unknown percentage), and others, might have a significant clinical impact on diagnoses, symptoms, and results among women with adenomyosis [12–19].

Finally, the reproductive outcomes of subfertile women with adenomyosis seemed to be varied greatly when different protocol of IVF/ICSI is arranged. Subfertile women with adenomyosis who were treated with a long-protocol of GnRH agonist in the IVF/ICSI cycles, women with and without adenomyosis seemed to have the similar clinical pregnancy rate, with the common RR of clinical pregnancy per patient of 1.05 (95% CI 0.75–1.48) after pooling data from two studies [20,21]. By contrast, the clinical pregnancy rate seemed to be reduced significantly when a short protocol was used in subfertile women with adenomyosis during the IVF/ICSI cycles, with the RR of 0.58 (95% CI 0.38–0.88) in the summarized data of four studies [22–25].

All of them are often overlooked in the study of the relationship between adenomyosis and its clinical observation. Therefore, it is not easy to explore or study the correlation between adenomyosis and fertility problems. We would like to conduct an extensive review of this topic, including recent publications, to highlight the potential influence of adenomyosis on reproduction.

Adenomyosis and fertility

A recent publication by Vercellini et al [11] tried to answer the following question—is adenomyosis associated with assisted reproductive techniques (ART), including *in vitro* fertilization and

intracytoplasmic sperm injection (IVF/ICSI)? To answer this, a systematic review and meta-analysis was performed. A summary of the findings from Dr. Vercellini et al's [11] study and Dr. Benagiano et al's [7] article on reproductive outcomes in women with/without adenomyosis are shown in Table 1. Compared with the reproductive performance of women without adenomyosis, women with adenomyosis seemed to have a lower implantation rate per embryo transfer, lower clinical pregnancy rate, and lower live birth or ongoing pregnancy rate, but a higher spontaneous abortion rate. Women with adenomyosis had a significant decrease in the clinical pregnancy rate (RR 0.72, 95% CI 0.55–0.95) and had a twofold risk of miscarriage (RR 2.12, 95% CI 1.20–3.75), suggesting that the adenomyotic uterine environment increases the risk of miscarriage independently of oocyte and embryo quality. The overall live birth rate was significantly impaired in women with adenomyosis (RR 0.70, 95% CI 0.56–0.87). Taken altogether, women with adenomyosis had a significantly decreased clinical pregnancy rate and a significantly increased miscarriage rate, contributing to the significant decrease in the final live birth rate (Table 1), and suggesting that there is a strong association between adenomyosis and fertility.

Indications

Although the above-mentioned evidence seemed to show that adenomyosis might be associated with a negative impact on women's fertility, management of these women with adenomyosis-associated subfertility is highly controversial, resulting in absence of consensus of conservative surgery in the management of these subfertile women with adenomyosis: (1) we do not know who will benefit from medical treatment alone, such as ART, and who will benefit from conservative surgery; (2) we do not know when is the appropriate time for patients to ask for an expert's opinion; and (3) we do not know whether there will be an improvement in reproductive performance after the use of medical and/or surgical management.

Before considering the benefits of conservative surgery in the management of these subfertile women with adenomyosis, we could not overlook the age factor, because it might be the most critical factor of fertility. It is well known that fertility declines after 35 years of age, and the chance of miscarriage increases [26].

Unfortunately, uterine adenomyosis is frequently thought to be a disease of women in their late reproductive age (40–50 years) and these women often have finished their childbirth and it is hard

to convince the physicians that these younger and nulliparous subfertile women have adenomyosis [27].

A recent study from Japan showed that the clinical pregnancy rates among women with adenomyosis treated with conservative surgery were 41.3% in those aged ≤ 39 years and 3.7% in those aged ≥ 40 years, suggesting an adverse impact of age on clinical pregnancy [odds ratio (OR) 0.77, 95% CI 0.67–0.88, $p = 0.002$] [14]. Factors associated with clinical pregnancy included history of IVF treatments (OR 6.22) and posterior wall involvement (OR 0.18). Therefore, the authors recommended that conservative surgery for adenomyosis could be a beneficial treatment for women who experienced IVF treatment failures, especially those aged ≤ 39 years [14]. In our previous study assessing factors associated with future pregnancy and successful delivery in subfertile women with adenomyosis after combination therapy with conservative surgery and gonadotropin releasing hormone agonist (GnRH agonist), we found that age was an important factor associated with future successful delivery. As a result, we recommended that caution should be taken in considering the maintenance of future fertility in older women treated with conservative surgery [17].

In summary, we believe that the clinical evaluation and management of subfertile women with adenomyosis might be similar to the strategy from other reasons, such as Asherman's syndrome and endometriosis [28,29]. Our suggestion is shown in Figure 1. The first step is routine infertility workup. Without the use of IVF/ICSI in the management of women with adenomyosis when these women have normal ovarian function and normal uterine structure, a long protocol should be taken into consideration, because these long-protocol GnRH agonist therapies resulted in a few cases of successful pregnancy and live birth [4]. However, it is important to emphasize that all pregnancies occurred within 12 months after completing therapy, or immediately to 6 months after the return of the first menstruation when these subfertile women were treated with a long-protocol GnRH agonist treatment, suggesting that the pregnancy window is relatively limited and short [9]. Therefore, a further active management should be switched promptly if pregnancy does not occur within the 1st year after completing therapy or within 6 months after the return of menstruation, and this active management might include repeating the use of a long protocol of GnRH agonists without ART or a long protocol of GnRH agonist suppression-based IVF/ICSI should be attempted with all women [30], if they cannot become pregnant through natural cycles (Figure 1).

After ART treatment, if patients still fail to become pregnant and are relatively young (≤ 39 years of age), conservative surgery might be an alternative. It is of utmost importance to ensure the definite diagnosis of adenomyosis and assess the accurate location and the size of the adenomyosis focus preoperatively. Complete removal of focal adenomyosis (adenomyoma) and conservative cytorreductive surgery of diffuse adenomyosis without marked distortion of the uterine structure is quite likely to improve the tumor-related symptoms or morbidity. As it has been reported that ART methods achieve increased pregnancy rates compared with natural cycles after conservative surgery for adenomyosis [31], IVF/ICSI should be arranged for these women after conservative surgical treatment. In the majority of studies that dealt with pregnancy after conservative surgery for adenomyosis, attempts at conception were suggested at least 3 months after the intervention [32,33].

Complications

Before discussing complications after conservative surgery for adenomyosis, the potential consequences of adenomyosis in terms of major obstetrical morbidity might need more research. However, it is not easy to investigate the relationship between adenomyosis

Table 1
Summary of clinical pregnancy outcomes in subfertile women with adenomyosis undergoing ART (IVF/ICSI) treatment.

Parameters	Adenomyosis (%)	Controls (%)
Implantation rate per ET	18.8–31.0	≥ 30
Clinical pregnancy rate*	19.0–59.5 (123/304, 40.5)	26.3–74.2 (628/1262, 49.8)
Miscarriage rate ^a	10.0–66.7 (77/241, 32.0)	2.8–46.7 (97/687, 14.1%)
Live birth rate ^{a,b}	10.5–39.6 (88/328, 26.8)	20.8–61.6 (123/331, 37.1)

Data are presented as range and cumulative data.

ART = assisted reproductive techniques; ET = embryo transfer; IVF/ICSI = *in vitro* fertilization and intracytoplasmic sperm injection.

Note. From "Adenomyosis: a life-cycle approach," by G. Benagiano, I. Brosens, and M. Habiba, 2015, *Reprod Biomed Online*, 30, p. 220–32. Copyright 201X, Name of Copyright Holder and from "Uterine adenomyosis and *in vitro* fertilization outcome: a systematic review and meta-analysis," by P. Vercellini, D. Consonni, D. Drudi, B. Bracco, M.P. Frattaruolo, and E. Somigliana, 2014, *Hum Reprod*, 29, p. 964–77. Copyright 201X, Name of Copyright Holder. Adapted with permission.

^a Data obtained from difference sources contribute to the heterogeneity of the data presentation.

^b Live birth rate includes ongoing pregnancy rate.

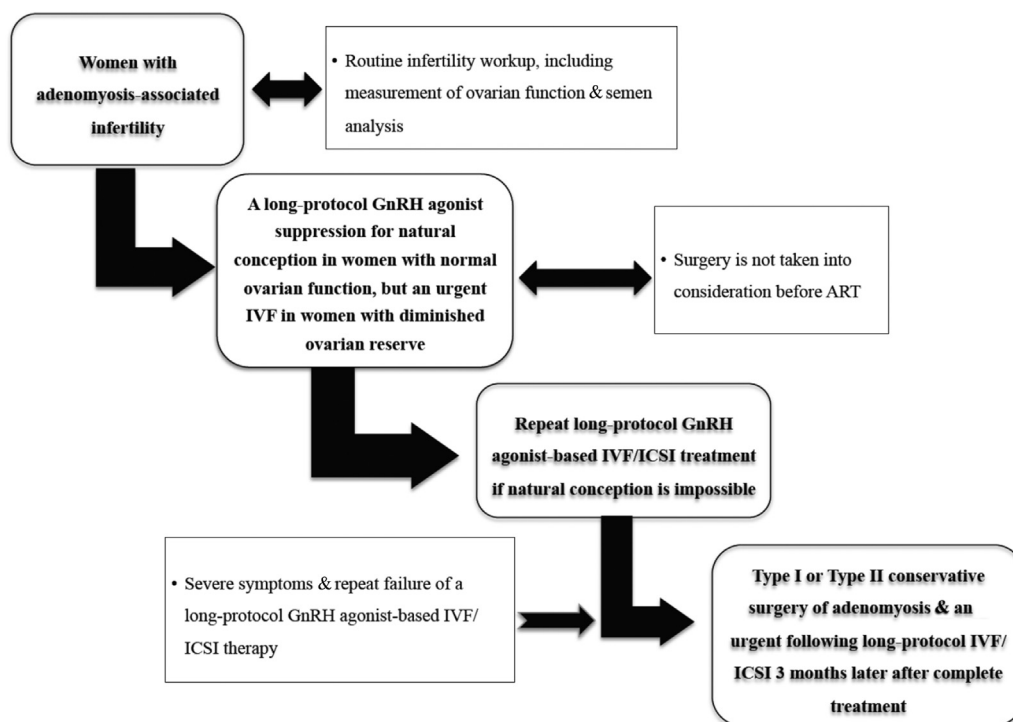


Figure 1. Algorithm for management of women with adenomyosis-associated infertility. ART = assisted reproductive techniques; GnRH agonist = gonadotropin releasing hormone agonist; IVF/ICSI = *in vitro* fertilization and intracytoplasmic sperm injection.

and major obstetrical morbidity, partly because few data on the epidemiology of adenomyosis in pregnancy are available, and partly because it is uncertain how many pregnancies occur in women with adenomyosis. In fact, only a few reported adenomyosis-related complications were found in a literature review. These included rapid growth of adenomyosis or adenomyoma in pregnancy, spontaneous miscarriage, preterm birth, intrauterine growth restriction, preeclampsia, obstetric hemorrhages, and spontaneous rupture of an unscarred uterus during pregnancy or labor [7,34,35]. In this regard, it has been suggested that alterations in the inner myometrium of women with adenomyosis may result in defective remodeling of the spiral arteries during the decidualization process, leading to vascular resistance and an increased risk of defective deep placentation [11]. However, there is no doubt that most women with adenomyosis will have an uneventful delivery, that the influence of the disease on the course of pregnancy is unclear, and that it is difficult to provide any useful and specific intervention for women with adenomyosis during pregnancy. Overemphasizing the disease status of adenomyosis with these women who attempt to conceive and/or who are pregnant may not be necessary.

For those who would like to become pregnant, conservative surgery might result in additional risk of adhesion, deformity of the uterus, occlusion of the Fallopian tubes and risk of total and/or subtotal hysterectomy, similar to any kind of uterine surgery, including myomectomy [36–39]. In this situation, infertility might be much more exacerbated, and the ability to get pregnant might be further compromised. Of course, ART could overcome some of the above-mentioned sequels.

For the plan of labor, elective cesarean section after conservative surgery for adenomyosis and/or adenomyomectomy for adenomyoma seems a better choice for patient safety [31]. Although a few case reports showed the possibility of successful vaginal deliveries in women with adenomyosis after conservative surgery, the majority of cases were completed by cesarean section. It is recognized

that uterine ruptures might occur during pregnancy or labor after conservative surgery for adenomyosis [31]. Furthermore, it is speculated that subsequent uterine scars may conceal dense residual adenomyotic foci, and as a consequence, the tensile strength of the uterus may decline, leading to possible rupture of the pregnant uterus [38].

Pregnancy outcome

In 2000, we reported three women aged older than 30 years old with > 60 months of unexplained infertility, who were treated with a combination of cytoreductive surgery and GnRH agonist management, and all three had a successful pregnancy and finally a term birth by cesarean section [32]. At that time, it was still hard to convince audiences regarding the value of conservative surgery in the management of subfertile women with adenomyosis. However, much more evidence has been obtained to support the potential value of conservative surgery for adenomyosis.

In a recent review by Grimbizis et al [31], the authors found that this surgical approach could provide significantly improved symptom control in > 81% (dysmenorrhea control) and 50% (menorrhagia control) of women with adenomyosis and/or adenomyoma. In addition, pregnancy rates appeared to be > 46% in women treated with Type II conservative cytoreductive surgery, and 60% in women treated with Type I adenomyomectomy surgery; two-thirds of the women treated with Type II surgery and more than four-fifths of the women treated with Type I surgery had a successful delivery (Table 2). Detailed information on Type I and Type II surgery was introduced in our previous publication [6]. In brief, in the Type I procedure, complete resection of adenomyosis (also called adenomyomectomy), all myomectomy procedures can be applied, with the only difference that the margin between the tumor and the normal myometrium might not be as clear as with adenomyomectomy [6]. In the Type II procedure, conservative

Table 2

Summary of pregnancy outcomes in subfertile women with adenomyosis after different types of conservative surgery treatment.

Surgical methods	Type I (n/n, %) ^a	Type II (n/n, %) ^a
Conception by nature	72/147 (49.0)	15/32 (46.9)
Conception by ART	17/147 (11.6)	0
Total conception	89/147 (60.5)	15/32 (46.9)
Miscarriage	15/89 (16.9)	4/15 (26.7)
Preterm delivery	7/89 (7.9)	0
Term delivery	66/89 (74.2)	10/15 (66.7)
Total delivery	73/89 (82.0)	10/15 (66.7)

ART = assisted reproductive techniques.

Note. From "Adenomyosis: a life-cycle approach," by G. Benagiano, I. Brosens, and M. Habiba, 2015, *Reprod Biomed Online*, 30, p. 220–32. Copyright 201X, Name of Copyright Holder and from "Endometriosis and infertility: pathophysiology and management," by D. de Ziegler, B. Borghese, and C. Chapron. *Lancet* 2010;376:730–8. Copyright 201X, Name of Copyright Holder. Adapted with permission.

^a Type I and Type II: conservative surgery for adenomyosis and the detailed information are reported in a previous study [6]. In brief, Type I conservative surgery involves complete and total excision of adenomyotic foci of the uterus, and Type II conservative surgery is an attempt to remove all visible adenomyotic foci, which are widely distributed within the uterus, although this is nearly impossible. The results of Type II conservative surgery include optimal and suboptimal cytotreduction.

cytoreductive uterine-sparing surgery was used with optimal or suboptimal excision of adenomyotic foci in the uterus [6].

In the domestic data, women with localized adenomyosis after adenomyomectomy treatment had a pregnancy rate that ranged from 48.2% to 77.5%, and had a successful delivery rate that ranged from 26.8% to 69.0% [17,33]. Although conservative surgery might not have a similarly promising effect on reproductive performance in women with diffuse-type adenomyosis, the pregnancy rate was > 30–40% in women with extensive adenomyosis after conservative surgery, amounting to nearly one-fourth to one-third of the women who had a successful delivery [9,32,40]. Compared with the 6 months of subfertile women with adenomyosis after medical treatment with a long protocol GnRH agonist, spontaneous pregnancy might occur 36 months after complete conservative surgery, suggesting that the therapeutic effect of conservative surgery might maintain longer than that of medical treatment. Taken together, conservative surgery might be an alternative if subfertile women with adenomyosis fail to become pregnant after an active treatment, including a long protocol GnRH agonist treatment and IVF/ICSI (Figure 1).

Adenomyosis appears to have a detrimental impact on reproductive performance in terms of decreased clinical pregnancy rate and increased abortion rate; however, many potential confounding factors could not be adequately assessed. Infertile women should be evaluated for the possibility of adenomyosis, and further discussions and therapeutic plans should be integrated with several other variables that may have an impact on the likelihood of success [11]. Among these, conservative surgery for symptomatic uterine adenomyosis and its variants appears to be feasible and efficacious, although data supporting this type of intervention are still suboptimal [41]. Therefore, the therapeutic strategy might follow the guideline of infertility evaluation (Figure 1).

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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