

# Effects of adenomyosis on in vitro fertilization treatment outcomes: a meta-analysis

Grace Younes, M.D. and Togas Tulandi, M.D., M.H.C.M.

Department of Obstetrics and Gynecology, McGill University, Montreal, Quebec, Canada

**Objective:** To systematically review and summarize the existing evidence related to the effect of adenomyosis on fertility and on in vitro fertilization (IVF) clinical outcomes, and to explore the effects of surgical or medical treatments.

**Design:** Meta-analysis.

**Setting:** Not applicable.

**Patient(s):** An electronic-based search was performed with the use of the following databases: Pubmed, Embase, Ovid Medline, Cochrane Central Register of Controlled Trials, and Google Scholar, identifying all related articles up to November 2016. We included 11 comparative studies that evaluated the clinical outcomes of IVF treatments in women with (519 patients) and without (1,535 patients) adenomyosis diagnosed with the use of magnetic resonance imaging or transvaginal ultrasound. We also separately evaluated four articles comparing fertility outcomes in two groups of infertile adenomyotic patients untreated and treated surgically or medically with the use of GnRH agonist (GnRHa).

**Intervention(s):** None.

**Main Outcome Measure(s):** Primary outcome: clinical pregnancy rate after IVF. Secondary outcomes: rates of implantation, ongoing pregnancy, live birth, miscarriage, and ectopic pregnancy. The summary measures were expressed as odds ratio (OR) and 95% confidence interval (CI).

**Result(s):** The rates of implantation, clinical pregnancy per cycle, clinical pregnancy per embryo transfer, ongoing pregnancy, and live birth among women with adenomyosis were significantly lower than in those without adenomyosis. The miscarriage rate in women with adenomyosis was higher than in those without adenomyosis. It appears that surgical treatment or treatment with GnRHa increases the spontaneous pregnancy rate in women with adenomyosis.

**Conclusion(s):** Adenomyosis has a detrimental effect on IVF clinical outcomes. Pretreatment with the use of long-term GnRHa or long protocol could be beneficial. (Fertil Steril® 2017;108:483–90. ©2017 by American Society for Reproductive Medicine.)

**Key Words:** Adenomyosis, adenomyoma, infertility, meta-analysis, in vitro fertilization

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**A**denomyosis is a benign disorder where basal endometrial glands and stroma are found in the myometrium with reactive hyperplasia of the surrounding smooth muscle myometrial cells (1–3). Traditionally, the diagnosis was made by means of histopathologic examination. With the evolution of magnetic resonance imaging (MRI) and high-quality transvaginal ultrasound (TVUS), today the diagnosis can be made with a level of accuracy of

80%–90% without the need for excisional surgery (4–7).

Adenomyosis is associated with enlarged uterus, pelvic pain, excessive vaginal bleeding, and decreased quality of life (8). It has also been linked with poor obstetrical outcomes. In a matched case-control study, women with adenomyosis had increased preterm delivery and preterm premature rupture of membrane (9). However, its effect on fertility remains debatable.

Several theories have been proposed, including impaired uterotubal transport (10), reduced sperm function due to high levels of nitric oxide in the uterine cavity (11), impaired implantation, altered uterine contractility, and many others (12–19).

Results of studies evaluating the effects of adenomyosis on the outcome of in vitro fertilization (IVF) treatment have been mixed (20–30). A previous meta-analysis of nine articles concluded that adenomyosis might have a negative impact on IVF treatment outcomes. It decreases the rates of implantation and clinical pregnancy and increases the miscarriage rate. The heterogeneity among the studies in that meta-analysis was high (31).

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Reprint requests: Grace Younes, M.D., McGill Reproductive Center, 888 Boul de Maisonneuve East #200, Montreal, Quebec H2L 4S8 (E-mail: [graceyounes@gmail.com](mailto:graceyounes@gmail.com)).

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Adenomyosis in infertile women can be treated surgically or medically with the use of GnRH agonist (GnRHa). Surgical excision is usually reserved for focal adenomyosis or adenomyoma. GnRHa has an antiproliferative effect on the tissue, induces apoptosis, and reduces inflammatory reaction and angiogenesis (32). The use of GnRHa treatment for adenomyosis and its effect on fertility is mostly based on case reports (33–37). Two retrospective studies suggest that long-term GnRHa treatment in women with adenomyosis before frozen-embryo transfer is associated with increased clinical pregnancy rate (38, 39). However, to date, there is insufficient evidence to support the preference of one treatment for adenomyosis over another.

The purpose of the present review was to determine the effect of adenomyosis on fertility and on IVF clinical outcomes, and to explore the effects of surgical or medical treatments.

## MATERIAL AND METHODS

### Search Strategy

We conducted an electronic-based search with the use of the following databases: Pubmed, Embase, Ovid Medline, Cochrane Central Register of Controlled Trials, and Google Scholar. The following medical subject heading terms, keywords, and their combinations were used: “adenomyosis,” “adenomyoma,” “in vitro fertilization,” “assisted reproductive technology,” “implantation rate,” “pregnancy,” “miscarriage,” “live birth,” “infertility,” “subfertility,” “treatment.” Both authors assessed each trial independently and had no discrepancies. The search was limited to full-length manuscripts published in English in peer-reviewed journals up to November 2016. The reference lists of all included articles and relevant reviews and meta-analyses were reviewed to search for other relevant articles.

### Study Selection

We included all comparative studies that compared clinical outcomes of IVF treatments between two infertile groups: women with adenomyosis diagnosed by MRI or TVUS, and those without the diagnosis of adenomyosis.

We also evaluated separately all articles comparing fertility outcomes in two groups of infertile adenomyosis patients untreated and treated surgically or medically. We excluded review articles, case reports and case series, video reports, and articles written in languages other than English.

### Data Extraction and Analysis

The review was made in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement (Supplemental Fig. 1; available online at [www.fertstert.org](http://www.fertstert.org)). All articles were reviewed and the following data recorded: year of publication, study design, study population, numbers of patients and cycles, diagnostic method, treatment protocol, and rates of implantation, clinical pregnancy, ongoing pregnancy, live birth, miscarriage, and ectopic pregnancy. Methodologic

quality assessment of nonrandomized studies was made for potential risk of bias with the use of the Newcastle-Ottawa scale for observational studies (Supplemental Table 1; available online at [www.fertstert.org](http://www.fertstert.org)). Clinical pregnancy rate and other secondary clinical outcomes are expressed as odds ratio (OR) and 95% confidence interval (CI). The meta-analysis was done with the use of a fixed-effect model.

## RESULTS

Of a total 307 articles, we included 15 studies (Supplemental Fig. 1): 11 observational studies on clinical outcome of IVF (Table 1) and four retrospective studies evaluating the effects of surgical or medical treatment of adenomyosis on fertility (Table 2). Of the 11 studies on IVF outcome, five were prospective cohort studies (20, 22, 25, 26, 29) and six were retrospective cohort studies (21, 23, 24, 27, 28, 30). These studies compared the clinical outcomes of IVF treatment among infertile women with and without adenomyosis. The primary outcome was clinical pregnancy rate, and the secondary outcomes were the rates of implantation, miscarriage, ongoing pregnancy rate, live birth, and ectopic pregnancy. Two of the four retrospective studies compared fertility outcomes of infertile women with adenomyosis treated by means of conservative surgery and GnRHa or with the use of GnRHa alone. The authors examined the cumulative pregnancy rate 3 years following the treatment (40, 41). The other two studies compared infertile women with adenomyosis treated with the use of long-term GnRHa before IVF treatment and those without GnRHa treatment (38, 39).

We evaluated the quality of the studies based on the Newcastle-Ottawa scale for observational and nonrandomized studies (Supplemental Tables 1 and 2; available online at [www.fertstert.org](http://www.fertstert.org)). All studies had a score that ranged from 5 to 8. All studies had a good selection of participants except one that included only women with colorectal endometriosis (20). In all studies, it was difficult to assess whether there was loss of follow-up. In eight studies, there was no adequate comparability of study groups (20, 22, 25, 28–30, 40, 41).

The definition of clinical pregnancy differed between studies: ultrasound evidence of fetal cardiac activity (22, 23, 27, 28, 38) and intrauterine gestational sac at 5–6 weeks of gestation (20, 26, 39), 7–8 weeks of gestation (21, 24), and unspecified time (25, 29). Three studies did not define clinical pregnancy (30, 40, 41). Martinez-Conejero et al. followed the patients until term (30), and five studies reported live births (21, 23, 26, 27, 29). All 11 studies in the meta-analysis evaluated IVF clinical outcomes among infertile women with and without adenomyosis.

The main characteristics of the included studies are listed in Table 1. Although all of the studies included infertile patients and most included infertile women with various causes of infertility, three studies included specific populations, such as patients with colorectal endometriosis (20), women undergoing oocyte donation cycles (30), and infertile women with surgically proven endometriosis (28). The study populations included different percentages of women with endometriosis

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