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

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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 withf 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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Adenomyosis 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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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). 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). 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). 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

TABLE 1

Main characteristics of the included studies on adenomyosis and its effect on IVF treatment outcomes.

Authors	Study design	Study population	Age	No. of patients with adenomyosis	No. of patients without adenomyosis	Method of diagnosis	Treatment protocol	No. of IVF cycles
Ballester et al. (2012) (20)	Prospective multicenter study	Infertile women with colorectal endometriosis and no previous surgery for deep infiltrating endometriosis or adenomyosis undergoing IVF/ICSI treatments	23–42, median 33	21	54	MRI	• Long protocol with GnRHa • Short protocol with GnRHa • Antagonist protocol	1–3
Benaglia et al. (2014) (26)	Prospective cohort study	Infertile women undergoing first IVF/ICSI treatment	≤42	49	49	TVUS	• Long protocol with GnRHa • Short protocol with GnRHa • Antagonist protocol	1
Chiang et al. (1999) (29)	Prospective cohort study	Infertile women undergoing TVUS before IVF treatment	Mean 36	19	144	TVUS	• Long protocol with GnRHa • Short protocol with GnRHa	1
Costello et al. (2011) (27)	Retrospective cohort study	Infertile women for various causes undergoing first IVF/ICSI treatment	18–42	37	164	TVUS	Long protocol with GnRHa	1
Martinez Conejero et al. (2011) (30)	Retrospective cohort study	Infertile women undergoing oocyte donation cycle	39–42, mean 40.5	152 patients, 328 cycles	147 patients, 331 cycles	TVUS	Oocyte donation protocol with HRT	1–3
Maubon et al. (2010) (25)	Prospective cohort study	Infertile women undergoing pelvic MRI before IVF treatment	21–43, mean 33	39	113	MRI	• Long protocol with GnRHa • Antagonist protocol	1–3
Mijatovic et al. (2010) (28)	Retrospective cohort study	Infertile women with surgically proven endometriosis undergoing first IVF/ICSI cycle after long-term GnRHa treatment	Mean 33	20	54	TVUS	≥3 mo GnRHa (mean 5 mo, range 3–26 mo)	1
Salim et al. (2012) (22)	Prospective cohort study	Infertile women undergoing first IVF/ICSI cycle	Mean 34	19	256	TVUS	Long protocol with GnRHa	1
Thalluri et al. (2012) (24)	Retrospective cohort study	Infertile women undergoing first IVF/ICSI treatment and single transfer of a good-quality embryo	≤39	38	175	TVUS	Antagonist protocol	1

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TABLE 1

Continued.

Authors	Study design	Study population	Age	No. of patients with adenomyosis	No. of patients without adenomyosis	Method of diagnosis	Treatment protocol	No. of IVF cycles
Yan et al. (2014) (21)	Retrospective cohort study	Infertile women undergoing IVF/ICSI treatment with adenomyosis diagnosed by TVUS	≤42, mean 34	77	77	TVUS	• Long GnRHa protocol • Short GnRHa protocol • Ultrashort agonist protocol • Mild stimulation	1
Youm et al. (2011) (23)	Retrospective cohort study	Infertile women undergoing IVF for various causes	≤40	48[a] (73 cycles)	302 (397 cycles)	TVUS	Short GnRHa protocol	1–2

Note: GnRHa = gonadotropin-releasing hormone agonist; ICSI = intracytoplasmic sperm injection; HRT = hormone replacement therapy; IVF = in vitro fertilization; MRI = magnetic resonance imaging; TVUS = transvaginal ultrasound.
[a] Only the group with thickness >2.5 cm was considered in this meta-analysis.

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TABLE 2

Studies evaluating the effects of treatment of adenomyosis on fertility/IVF outcome.

Authors	Study design	Study population	Patient group A (n)	Patient group B (n)	Method of diagnosis	Treatment	Outcome
Al Jama et al. (2011) (40)	Retrospective cohort study	Infertile patients with adenomyosis	18 patients treated with surgery + GnRHa	22 patients treated with GnRHa alone	TVUS and MRI	6 courses of GnRHa	Spontaneous pregnancy within 3 y
Wang et al. (2009) (41)	Retrospective cohort study	Patients with adenomyosis and unexplained infertility	28 treated with surgery ± GnRHa therapy	37 treated with 6 mo GnRHa alone	TVUS and pathology	Surgery vs. 6 mo GnRHa	Spontaneous pregnancy within 3 y
Niu et al. (2013) (38)	Retrospective cohort study	Infertile women with adenomyosis undergoing frozen-embryo transfer	194 treated with GnRHa and HRT	145 treated with HRT alone	TVUS	3.75 mg leuprolide acetate, 28 days later 1.875 mg, and 21 days later plus HRT; or HRT alone	Clinical pregnancy after 1 cycle
Park et al. (2016) (39)	Retrospective cohort study	Infertile women with adenomyosis undergoing fresh- or frozen-embryo transfer	87 women/105 cycles with GnRHa treatment before fresh transfer	116 women/147 cycles without GnRHa treatment before fresh transfer	TVUS	Goserelin 3.75 mg for 2–3 months	Clinical pregnancy after 1–2 IVF cycles

Note: Abbreviations as in Table 1.

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as a diagnosis for infertility. Two studies included a population of only women with endometriosis (20, 28). Table 1 presents the 11 studies (2,054 patients) included in the meta-analysis, consisting of 519 patients with and 1,535 without adenomyosis. Effects of surgical or medical treatment on fertility or IVF outcome are presented in Table 2.

Spontaneous Pregnancy Rate After Surgery

Two studies examined the effect of a combined treatment with the use of conservative surgery and GnRHa versus GnRHa treatment alone (40, 41). It appears that surgery is associated with increased pregnancy rate (Fig. 1A; OR 6.22, 95% CI 2.34–16.54). However, the number of samples in the studies were small.

Focal Versus Diffuse Adenomyosis

Two studies compared the effects of focal versus diffuse adenomyosis on IVF outcome (26, 39). The pooled results gave an OR of 1.36 favoring focal adenomyosis; however, the CIs were 0.67–2.75 (Fig. 1B).

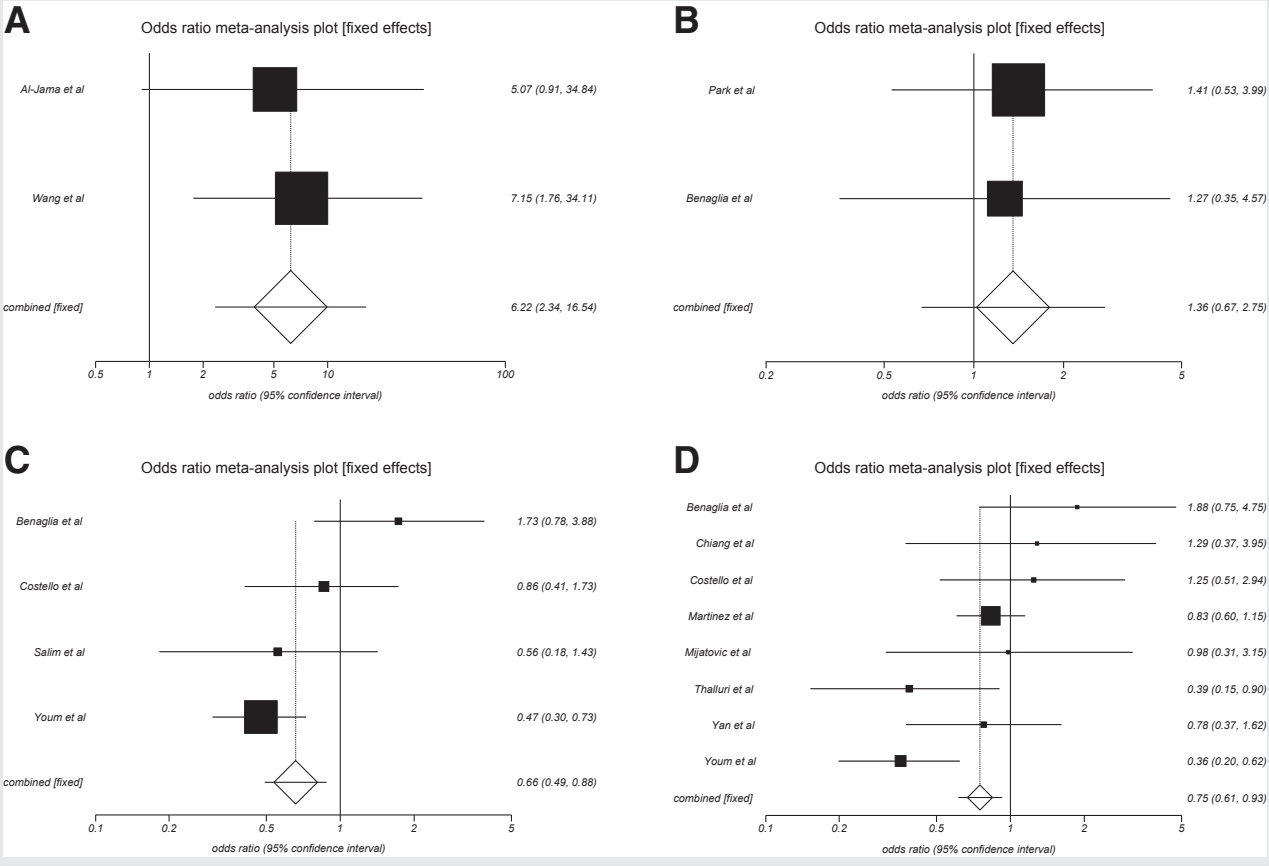
Implantation and Pregnancy Outcome

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 among those without adenomyosis (Figs. 1C, 1D, and 2). The miscarriage rate in women with adenomyosis was higher than in those without adenomyosis (Fig. 2D; OR 2.2, 95% CI 1.53–3.15). Live birth rate per cycle was reported in five studies (21, 23, 26, 27, 29). The presence of adenomyosis was associated with a 41% decrease in live birth rate (Fig. 2C; OR 0.59, 95% CI 0.42–0.82).

Effects of GnRHa Pretreatment before IVF

The effects of GnRHa treatment before IVF in women with adenomyosis were evaluated in two studies. One study compared combined GnRHa with add-back or add-back

FIGURE 1



(**A**) Cumulative spontaneous clinical pregnancy rate in women who underwent surgery for adenomyosis and who did not (favoring surgery). (**B**) Clinical pregnancy rates after fresh-embryo transfer in women with diffuse (*left of vertical line*) and focal adenomyosis (*right of vertical line*). (**C**) Implantation rates in women without and with adenomyosis. (**D**) Clinical pregnancy rate per embryo transfer in women without and with adenomyosis.

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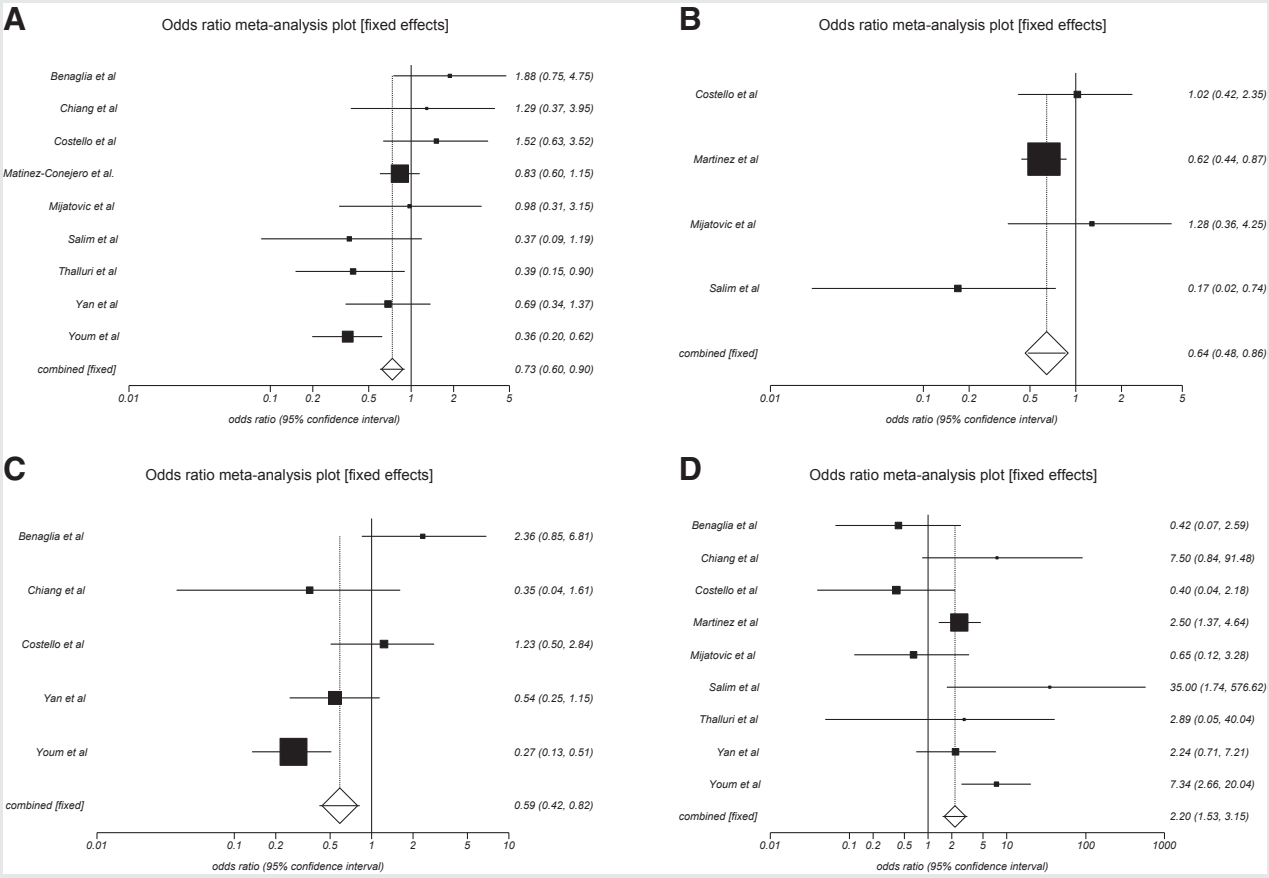
FIGURE 2



(**A**) Clinical pregnancy rate per cycle in women without and with adenomyosis. (**B**) Ongoing pregnancy rate per cycle in women without and with adenomyosis. (**C**) Live birth rate per cycle in women without and with adenomyosis. (**D**) Miscarriage rate in women without and with adenomyosis.

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treatment alone before frozen-embryo transfer (38) and another compared GnRHa versus no treatment before fresh-embryo transfer (39). The results showed that pretreatment with GnRHa appears to be beneficial to the pregnancy rate.

DISCUSSION

Adenomyosis in infertile women has been encountered more frequently in recent years, owing to an improved diagnostic test with the use of high-resolution ultrasound as well as to the increasing age of women seeking fertility treatment. Yet the diagnosis of adenomyosis is often overlooked and not taken into consideration when planning an IVF treatment. In general, the detrimental effect of adenomyosis on IVF outcome appears to be related to reduced rates of implantation and pregnancy, increased risk of early pregnancy loss, and, as a result, a decrease in live birth rate. Our results are in agreement with those that have been previously published (31).

There are various hypotheses concerning the effects of adenomyosis on implantation, including impaired endometrium-myometrium interface, altered uterine peristaltic activity (12), altered endometrial-myometrial vascular growth, increased levels of prostaglandins in the ectopic endometrial epithelium (13, 14), higher expression of aromatase cytochrome P450 in the eutopic endometrium (15), decreased integrin $\beta 3$, osteopontin, and leukemia-inhibiting factor, and impaired HOXA-10 gene function during the implantation window (16–19).

It appears that diffuse adenomyosis fares worse than focal or localized adenomyosis (Fig. 1B). Furthermore, focal adenomyosis can be easily excised, leading to increased pregnancy rates (40, 41) (Fig. 1A). A few authors have also reported surgical treatment of diffuse adenomyosis (41). Instead of surgical excision, pre-IVF treatment with the use of GnRHa is certainly less invasive and more practical. GnRH receptors are present in the adenomyotic tissue, and GnRHa induces apoptosis and reduces the inflammatory reaction and angiogenesis (32). The results show that long-term GnRHa before IVF treatments improved the pregnancy rate (38, 39). However, there were only two studies available for our analysis. The disadvantages of using long-term GnRHa are longer ovarian stimulation and higher gonadotropin doses, especially in the fresh cycle. Its use before frozen cycles could be more cost-effective.

Although unavoidable, the studies included in our meta-analysis are heterogenous, which might cause some biases in the results. There were differences in the participants' age, duration of infertility, type of down-regulation protocol used, number and quality of the transferred embryos, number of IVF cycles performed, and the clinical outcomes assessed in the studies. In addition, the infertility diagnosis differed among studies. Two studies included only patients with endometriosis (20, 28), and in other studies the fraction of patients with endometriosis varied widely. The existence of endometriosis might be a confounding factor. It is unclear whether the concomittant endometriosis was untreated or treated either medically or surgically. However, even in the studies in which the proportion of patients with endometriosis was low (2.3% and 8%), the presence of adenomyosis led to a reduced clinical pregnancy rate and increased miscarriage rate (22, 24). In one study using a population with donor eggs, adenomyosis did not affect the rates of implantation and clinical pregnancy. However, the miscarriage rate was high and the term pregnancy rate was reduced (30).

Endometriosis is often found in women with adenomyosis, which might be an additional cause for infertility. There were two studies evaluating this issue (38, 39). In the study by Niu et al., concomitant endometriosis was found in 7.7% of the GnRHa group and in 6.9% of the non-GnRHa group, and the pregnancy rates were higher in the GnRHa group (38). Park et al. reported no endometriosis among their patients except adenomyosis, and the pregnancy rate was higher in the GnRHa group than in the nontreated group (39).

The IVF protocols in the studies varied including the use of long-term GnRHa before IVF treatment (28), long protocol (22, 27), short protocol (23), and antagonist protocol (24). Long-term GnRHa treatment and long protocol might have a therapeutic effect on adenomyosis and improve the IVF outcome. Indeed, a previous meta-analysis (31) found no effect of adenomyosis on the clinical outcome of a long protocol treatment. However, only two studies could be included in that analysis.

The definite diagnosis of adenomyosis is by histopathology of the uterine specimen. However, current imaging, such as MRI or TVUS, can detect adenomyosis to a certain extent. Perhaps those patients have a more severe degree of adenomyosis than those whose uterus contains microscopic adenomyosis only. The patients in the present meta-analysis suffered from clinically relevant adenomyosis. They are the women that we see in daily practice. In the context of infertility and IVF, treatment is indicated for women with symptomatic as well as asymptomatic adenomyosis. These women may benefit from prolonged GnRHa treatment or long protocol.

Different ultrasound criteria of adenomyosis have been used, including heterogeneous myometrial area, globular asymmetric uterus, irregular cystic spaces, myometrial linear striations, poor definition of endometrial myometrial junction, myometrial anterior posterior asymmetry and thickening of anterior and posterior myometrial wall, and increased or decreased echogenecity. The presence of adenomyoma is suggested by the presence of nonhomogeneous circumscribed areas in the myometrium with indistinct margins. MRI criteria of adenomyosis include myometrial mass with indistinct margins of primarily low intensity, diffuse or local widening of junctional zones on T2-weighted images with thickness >12 mm, uterine enlargement, and small hypointense myometrial spots (4–7).

The severity of adenomyosis was not stated in most studies. In any event, the present results demonstrate the deleterious effects of adenomyosis on the results of IVF. Our meta-analysis is an addition to the publication by Vercellini et al. (31), where they found that adenomyosis is associated with reduced pregnancy rates per cycle. We included two other studies, one of which was a well designed prospective cohort study. Furthermore, we analyzed clinical pregnancy rates per embryo transfer and per cycle as well as implantation rate, ongoing pregnancy, and live birth rate. Our results on clinical pregnancy rate and miscarriage rate support the earlier findings. In addition, we analyzed four studies on the treatment of adenomyosis surgically and medically.

We conclude that adenomyosis has a detrimental effect on IVF clinical outcomes. It reduces pregnancy and live birth rates and increases the miscarriage rate. It appears that pre-IVF treatment with the use of GnRHa down-regulation is beneficial. Further studies are needed.

REFERENCES

1. Brosens JJ, Barker FG, de Souza NM. Myometrial zonal differentiation and uterine junctional zone hyperplasia in the nonpregnant uterus. Hum Reprod Update 1998;4:496–502.
2. Leyendecker G, Herbertz M, Kunz G, Mall G. Endometriosis results from the dislocation of basal endometrium. Hum Reprod 2002;17:2725–36.
3. Ferenczy A. Pathophysiology of adenomyosis. Hum Reprod Update 1998;4:312–22.
4. Reinhold C, McCarthy S, Bret PM, Mehio A, Atri M, Zakarian R, et al. Diffuse adenomyosis: comparison of endovaginal US and MR imaging with histopathologic correlation. Radiology 1996;199:151–8.
5. Dueholm M, Lundorf E. Transvaginal ultrasound or MRI for diagnosis of adenomyosis. Curr Opin Obstet Gynecol 2007;19:505–12.
6. Meredith SM, Sanchez-Ramos L, Kaunitz AM. Diagnostic accuracy of transvaginal sonography for the diagnosis of adenomyosis: systematic review and meta-analysis. Am J Obstet Gynecol 2009;201:107.e1–6.
7. Maheshwari A, Gurunath S, Fatima F, Bhattacharya S. Adenomyosis and subfertility: a systematic review of prevalence, diagnosis, treatment and fertility outcomes. Hum Reprod Update 2012;18:374–92.
8. Botsis D, Kassanos D, Antoniou G, Pyrgiotis E, Karakitsos P, Kalogirou D. Adenomyoma and leiomyoma: differential diagnosis with transvaginal sonography. J Clin Ultrasound 1998;26:21–5.
9. Juang CM, Chou P, Yen MS, Twu NF, Horng HC, Hsu WL. Adenomyosis and risk of preterm delivery. BJOG 2007;114:165–9.
10. Kissler S, Hamscho N, Zangos S, Wiegratz I, Schlichter S, Menzel C, et al. Uterotubal transport disorder in adenomyosis and endometriosis—a cause for infertility. BJOG 2006;113:902–8.
11. Matalliotakis IM, Katsikis IK, Panidis DK. Adenomyosis: what is the impact on fertility? Curr Opin Obstet Gynecol 2005;17:261–4.
12. Kunz G, Leyendecker G. Uterine peristaltic activity during the menstrual cycle: characterization, regulation, function and dysfunction. Reprod Biomed Online 2002;4(Suppl 3):5–9.
13. Hickey M, Fraser I. Human uterine vascular structures in normal and diseased states. Microsc Res Tech 2003;60:377–89.
14. Ota H, Tanaka T. Stromal vascularization in the endometrium during adenomyosis. Microsc Res Tech 2003;60:445–9.
15. van Voorhis BJ, Huettner PC, Clark MR, Hill JA. Immunohistochemical localization of prostaglandin H synthase in the female reproductive tract and endometriosis. Am J Obstet Gynecol 1990;163(1 Pt 1):57–62.

16. Kitawaki J, Noguchi T, Amatsu T, Maeda K, Tsukamoto K, Yamamoto T, et al. Expression of aromatase cytochrome P450 protein and messenger ribonucleic acid in human endometriotic and adenomyotic tissues but not in normal endometrium. Biol Reprod 1997;57:514–9.
17. Xiao Y, Li T, Xia E, Yang X, Sun X, Zhou Y. Expression of integrin beta3 and osteopontin in the eutopic endometrium of adenomyosis during the implantation window. Eur J Obstet Gynecol Reprod Biol 2013;170:419–22.
18. Fischer CP, Kayisili U, Taylor HS. HOXA10 expression is decreased in endometrium of women with adenomyosis. Fertil Steril 2011;95:1133–6.
19. Xiao Y, Sun X, Yang X, Zhang J, Xue Q, Cai B, et al. Leukemia inhibitory factor is dysregulated in the endometrium and uterine flushing fluid of patients with adenomyosis during implantation. Fertil Steril 2010;94:85–9.
20. Ballester M, d'Argent EM, Morcel K, Belaisch-Allart J, Nisolle M, Darai E. Cumulative pregnancy rate after ICSI-IVF in patients with colorectal endometriosis: results of a multicentre study. Hum Reprod 2012;27:1043–9.
21. Yan L, Ding L, Tang R, Chen ZJ. Effect of adenomyosis on in vitro fertilization/intracytoplasmic sperm injection outcomes in infertile women: a retrospective cohort study. Gynecol Obstet Invest 2014;77:14–8.
22. Salim R, Riris S, Saab W, Abramov B, Khadum I, Serhal P. Adenomyosis reduces pregnancy rates in infertile women undergoing IVF. Reprod Biomed Online 2012;25:273–7.
23. Youm HS, Choi YS, Han HD. In vitro fertilization and embryo transfer outcomes in relation to myometrial thickness. J Assist Reprod Genet 2011;28:1135–40.
24. Thalluri V, Tremellen KP. Ultrasound diagnosed adenomyosis has a negative impact on successful implantation following GnRH antagonist IVF treatment. Hum Reprod 2012;27:3487–92.
25. Maubon A, Faury A, Kapella M, Pouquet M, Piver P. Uterine junctional zone at magnetic resonance imaging: a predictor of in vitro fertilization implantation failure. J Obstet Gynaecol Res 2010;36:611–8.
26. Benaglia L, Cardellicchio L, Leonardi M, Faulisi S, Vercillini P, Paffoni A, et al. Asymptomatic adenomyosis and embryo implantation in IVF cycles. Reprod Biomed Online 2014;29:606–11.
27. Costello MF, Lindsay K, McNally G. The effect of adenomyosis on in vitro fertilisation and intra-cytoplasmic sperm injection treatment outcome. Eur J Obstet Gynecol Reprod Biol 2011;158:229–34.
28. Mijatovic V, Florijn E, Halim N, Schats R, Hompes P. Adenomyosis has no adverse effects on IVF/ICSI outcomes in women with endometriosis treated with long-term pituitary down-regulation before IVF/ICSI. Eur J Obstet Gynecol Reprod Biol 2010;151:62–5.
29. Chiang CH, Chang MY, Shiau CS, Hou HC, Hsieh TT, Soong YK. Effect of a sonographically diffusely enlarged uterus without distinct uterine masses on the outcome of in vitro fertilization–embryo transfer. J Assist Reprod Genet 1999;16:369–72.
30. Martinez-Conejero JA, Morgan M, Montesinos M, Fortuño S, Meseguer M, Simón C, et al. Adenomyosis does not affect implantation, but is associated with miscarriage in patients undergoing oocyte donation. Fertil Steril 2011;96:943–50.
31. Vercellini P, Consonni D, Dridi D, Bracco B, Frattaruolo MP, Somigliana E. Uterine adenomyosis and in vitro fertilization outcome: a systematic review and meta-analysis. Hum Reprod 2014;29:964–77.
32. Khan KN, Kitajima M, Hiraki K, Fujishita A, Nakashima M, Ishimaru T, et al. Cell proliferation effect of GnRH agonist on pathological lesions of women with endometriosis, adenomyosis and uterine myoma. Hum Reprod 2010;25:2878–90.
33. Hirata JD, Moghissi KS, Ginsburg KA. Pregnancy after medical therapy of adenomyosis with a gonadotropin-releasing hormone agonist. Fertil Steril 1993;59:444–5.
34. Huang FJ, Kung FT, Chang SY, Hsu TY. Effects of short-course buserelin therapy on adenomyosis. A report of two cases. J Reprod Med 1999;44:741–4.
35. Huang WH, Yang TS, Yuan CC. Successful pregnancy after treatment of deep adenomyosis with cytoreductive surgery and subsequent gonadotropin-releasing hormone agonist: a case report. Zhonghua Yi Xue Za Zhi (Taipei) 1998;61:726–9.
36. Lin J, Sun C, Zheng H. Gonadotropin-releasing hormone agonists and laparoscopy in the treatment of adenomyosis with infertility. Chin Med J (Engl) 2000;113:442–5.
37. Silva PD, Perkins HE, Schauberger CW. Live birth after treatment of severe adenomyosis with a gonadotropin-releasing hormone agonist. Fertil Steril 1994;61:171–2.
38. Niu Z, Chen Q, Sun Y, Feng Y. Long-term pituitary downregulation before frozen embryo transfer could improve pregnancy outcomes in women with adenomyosis. Gynecol Endocrinol 2013;29:1026–30.
39. Park CW, Choi MH, Yang KM, Song IO. Pregnancy rate in women with adenomyosis undergoing fresh or frozen embryo transfer cycles following gonadotropin-releasing hormone agonist treatment. Clin Exp Reprod Med 2016;43:169–73.
40. Al Jama FE. Management of adenomyosis in subfertile women and pregnancy outcome. Oman Med J 2011;26:178–81.
41. Wang PH, Fuh JL, Chao HT, Liu WM, Cheng MH, Chao KC. Is the surgical approach beneficial to subfertile women with symptomatic extensive adenomyosis? J Obstet Gynaecol Res 2009;35:495–502.

SUPPLEMENTAL TABLE 1

Methodologic quality assessment of the included studies on adenomyosis and its effect on IVF treatment outcomes.

Author	Study design	Year of publication	Quality of evidence[a]	Comments
Ballester et al. (20)	Prospective multicenter	2012	5	The cohort is not a true representative of the average population, no comparability of cohorts, difficult to assess loss of follow-up
Benaglia et al. (26)	Prospective cohort study	2014	8	Difficult to assess loss of follow-up
Chiang et al. (29)	Prospective cohort study	1999	6	No adequate comparability of cohorts, Difficult to assess loss of follow-up
Costello et al. (27)	Retrospective cohort study	2011	8	Difficult to assess loss of follow-up
Martinez-Conejero et al. (30)	Retrospective cohort study	2011	7	No adequate comparability of cohorts, difficult to assess loss of follow-up
Maubon et al. (25)	Prospective cohort study	2010	6	No adjustment for confounding factors, difficult to assess loss of follow-up
Mijatovic et al. (28)	Retrospective cohort study	2010	6	No adjustment for confounding factors, difficult to assess loss of follow-up
Salim et al. (22)	Prospective cohort study	2012	6	No adjustment for confounding factors, difficult to assess loss of follow-up
Thalluri et al. (24)	Retrospective cohort study	2012	7	Difficult to assess loss of follow-up
Yan et al. (21)	Retrospective cohort study	2014	7	Difficult to assess loss of follow-up
Youm et al. (23)	Retrospective cohort study	2011	7	Difficult to assess loss of follow-up

[a] Quality of evidence assessed by means of the Newcastle-Ottawa scale for observational and nonrandomized studies, score 0–9.

Younes. Adenomyosis and IVF treatment outcomes. Fertil Steril 2017.

SUPPLEMENTAL TABLE 2

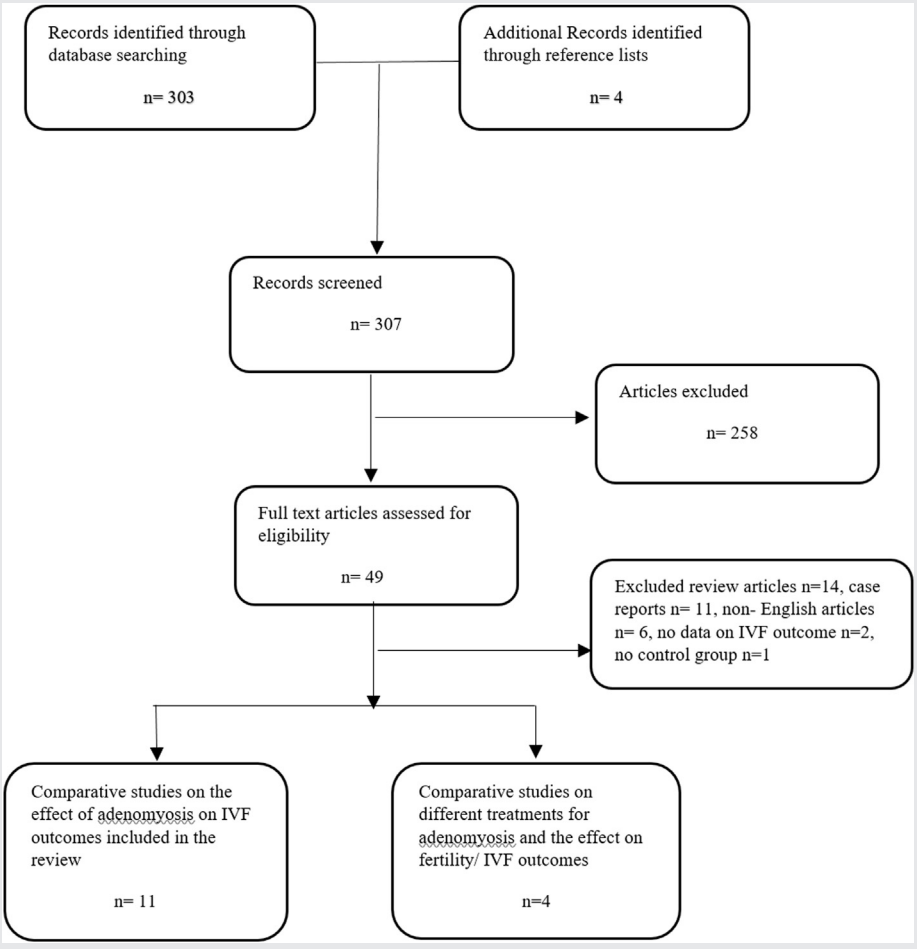
Methodologic quality assessment of the included studies on treatment of adenomyosis and its effect on fertility outcome.

Authors	Study design	Year of publication	Quality of evidence[a]	Comments
Al Jama et al. (40)	Retrospective	2011	6	No adjustment for confounding factors, difficult to assess loss of follow-up
Wang et al. (41)	Retrospective	2009	6	No adjustment for confounding factors, difficult to assess loss of follow-up
Niu et al. (38)	Retrospective	2013	8	Difficult to assess loss of follow-up
Park et al. (39)	Retrospective	2016	8	Difficult to assess loss of follow-up

[a] Quality of evidence assessed by means of the Newcastle Ottawa scale for observational and nonrandomized studies, score 0–9.

Younes. Adenomyosis and IVF treatment outcomes. Fertil Steril 2017.

SUPPLEMENTAL FIGURE 1



PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) 2009 flow diagram.

Younes. Adenomyosis and IVF treatment outcomes. Fertil Steril 2017.