Current Obstetrics and Gynecology Reports (2022) 11:198–224
https://doi.org/10.1007/s13669-022-00336-5

UTERINE FIBROIDS AND ENDOMETRIAL LESIONS (T. TULANDI, SECTION EDITOR)

Adenomyosis and Reproduction: a Narrative Review

Nicola Berlanda[1] · Agnese Donati[1] · Francesco Fedele[1] · Dhouha Dridi[1] · Giulia Emily Cetera[1] · Paolo Vercellini[1,2]

Accepted: 1 April 2022 / Published online: 22 April 2022

Abstract

Purpose of Review To investigate the reproductive outcome of infertile women with adenomyosis who undergo assisted reproductive technologies (ART) or conservative surgical treatment.

Recent Findings Among 23 studies evaluating the outcome of ART, 12 compared women with adenomyosis with controls, while 11 included only women with adenomyosis, accounting for a total of 3791 women with adenomyosis and 6841 controls. Compared to controls, patients with adenomyosis had a pregnancy rate of 39.4% vs 49.8%, a live birth rate of 29.9% vs 42.6%, a miscarriage rate of 26.3% vs 15.3%, and an implantation rate of 30.0% vs 31.6%, respectively. When comparing women receiving pre-treatment with GnRH agonists with those not receiving pre-treatment, 20% of studies reported an improved pregnancy rate, 20% reported a reduced miscarriage rate, and 50% reported an improved live birth rate. Among the 11 studies evaluating previous conservative surgical treatment on a total of 961 women, pregnancy rate was 38.1%, live birth rate was 63.7%, and miscarriage rate was 20.9%. A not negligible risk of placenta previa, placenta accreta, uterine rupture, and postoperative adhesions was reported.

Summary The available evidence shows that adenomyosis negatively affects reproductive outcome. Pre-treatment with GnRH agonists improved the live birth rate, but the magnitude of such improvement needs to be better defined in future studies. Conservative surgical treatment of both focal and diffuse adenomyosis was associated with a similar pregnancy rate to that of women who did not undergo surgery. However, an increase in live birth rate was observed after surgery.

Keywords Adenomyosis · Infertility · ART · GnRH agonists · Conservative surgery

Introduction

A causal relationship between adenomyosis and infertility has been repeatedly suggested [1, 2]. With women delaying their first pregnancy until their late 30s or early 40s, the diagnosis of adenomyosis in infertile patients is becoming increasingly frequent. The presence of adenomyosis may impair fertility by affecting the utero-tubal transport and by altering endometrial function and receptivity [2]. Moreover, several anomalies found in the junctional zone in patients with adenomyosis have been associated with poor reproductive performance, mainly due to perturbed uterine peristalsis. These patients also present with an altered decidualization and abnormally high levels of free radicals in the uterine milieu [1].

Accordingly, impaired fertility outcomes after ART have been reported in two systematic reviews [3, 4]. In one of them, the presence of adenomyosis was associated with a 28% reduction in the likelihood of clinical pregnancy in infertile women undergoing IVF/ICSI [3]. Moreover, the risk of miscarriage among these patients was more than doubled compared to controls. These results are in line with those of a more recent meta-analysis [4], in which adenomyosis resulted to be associated with a 41% decrease in live birth rate after IVF (OR 0.59, 95% CI 0.42–0.82), as well as a more than doubled risk of miscarriage (OR 2.2, 95% CI 1.53–3.15). However, reviews and meta-analyses on this subject are potentially biased by the intrinsic limitations of published studies. Younes and Tulandi [4] considered that

This article is part of the Topical Collection on *Uterine Fibroids and Endometrial Lesions*

✉ Nicola Berlanda
nicola.berlanda@policlinico.mi.it

[1] Gynecology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Via Commenda 12, 20122 Milan, Italy

[2] Department of Clinical Sciences and Community Health, Università degli Studi di Milano, Milan, Italy

studies were heterogeneous, with differences in women's age, duration of infertility, type of downregulation protocol used, number and quality of transferred embryos, and number of IVF cycles performed. Moreover, clinical outcomes, modality of infertility diagnosis, and the rate of concomitant endometriosis differed among studies, and some authors made no adjustment for confounding factors. Following the publication of Younes and Tulandi's review, which highlighted the importance of overcoming such limitations, further studies evaluating the reproductive outcome of women with adenomyosis undergoing either ART [5–8, 9••, 10, 11, 12••, 13–16] or conservative surgical treatment [17–20] have been published. Moreover, standardized and reproducible ultrasonographic and MRI diagnostic criteria for adenomyosis have been established [21, 22].

Given the availability of new and recent studies evaluating this issue, we sought to carry out a narrative review investigating the reproductive outcome of infertile women with adenomyosis who undergo ART or fertility-sparing surgical treatment.

Materials and Methods

An electronic database search on PubMed was performed with the objective of identifying all studies written in English and published between 2011 and 2021. We used the following combinations of terms such as "adenomyosis" AND "infertility", "adenomyosis" AND "IVF", and "adenomyosis" AND "conservative surgery" and found 442 articles. Three reviewers (AD, FF, and DD) independently reviewed titles, abstracts, and full article texts to identify eligible studies. Discrepancies were resolved by discussion. A total of 408 studies were excluded for the following reasons: 388 were deemed as not pertinent, while the remaining 20 lacked a control group, did not include proper outcomes, or were meta-analyses. The flow diagram of the literature search results is shown in Fig. 1.

Thirty-four studies were considered eligible for the present review. Among these, 23 evaluated the outcome of ART in infertile women with adenomyosis [5–8, 9••, 10, 11, 12••, 13–16, 23–33], and 11 evaluated the reproductive outcome of women with adenomyosis who had previously undergone conservative surgical treatment [17–20, 34–40]. Adenomyosis was diagnosed before conception in all studies. Diagnosis was performed by the means of transvaginal ultrasonography (TVUS) alone in 24 studies; 2D TVUS was used in 22 studies [5, 6, 8, 9••, 12••, 13, 16, 17, 19, 23–31, 36–38, 40], while 3D TVUS was used in two [10, 32]. In the remaining 10 studies, adenomyosis was diagnosed by means of TVUS and/or MRI [7, 11, 14, 15, 18, 20, 33–35, 39].

ART Studies

Five studies were prospective [9••, 10, 26, 29, 32], while the remaining 18 were retrospective [5–8, 11, 12••, 13–16, 23–25, 27, 28, 30, 31, 38]. A total of 22 studies evaluated autologous IVF/ICSI cycles, whereas the outcome of oocyte donation (OD) cycles was assessed in one study [24].

Women with adenomyosis were compared with women without adenomyosis in 12 articles [9••, 10, 13, 15, 16, 23, 24, 26, 27, 29, 30, 32]. In one study, patients with adenomyosis were compared with both women without adenomyosis and women with co-existent adenomyosis and endometriosis [24]. In Sharma et al.'s study, women with adenomyosis only and those with both adenomyosis and endometriosis were separately evaluated, and controls included women with endometriosis without adenomyosis as well as women with tubal infertility [16].

In four studies, women with adenomyosis who were pre-treated with GnRH agonists [6, 8, 28, 31] were compared with those not pre-treated, while in one study, pre-treatment with 52-mg 20-mg/d levonorgestrel-releasing IUD (LNG-IUD) was compared with no pre-treatment [14]. In Niu et al.'s study, women chose either treatment with GnRH agonists + HRT or a pure HRT protocol before frozen-thawed embryo transfer (FET) depending on their own preference [28]. Conversely, Park et al. compared the outcome of fresh embryo transfer (ET) cycles with or without pre-treatment with GnRH agonists with FET cycles with GnRH agonist pre-treatment [31]. In three further studies, all women were pre-treated with GnRH agonists [5, 12••, 16]. Three other studies reported data from subgroups of women undergoing pre-treatment with GnRH agonists [7, 15, 33]. Two studies compared ART outcomes in women with adenomyosis receiving a long vs ultra-long GnRH agonist protocol [9••, 11].

One study compared patients with adenomyosis and CA125 < 35 IU/ml with those with adenomyosis and CA125 > 35 IU/mL [33]. Li et al. compared women with adenomyosis who had a uterine volume < 99 cc with those with adenomyosis and a uterine volume > 99 cc [5]. Another study compared different values of myometrial thickness: < 2.00 cm, 2.00–2.49 cm, and ≥ 2.50 cm [25]. Iwasawa et al. compared women with different location and extension of adenomyosis within the myometrium, distinguishing between advanced (full thickness), extrinsic (located on the serosal side), and intrinsic (located on the endometrial side) adenomyosis [7]. Lastly, three studies compared outcomes in women with focal vs diffuse adenomyosis [11, 29, 31].

One study compared patients with adenomyosis with those with endometriosis [12••]. Only 11 studies reported the presence of endometriosis in enrolled women [5, 7, 8, 11, 12••, 15, 16, 23, 24, 30, 32].

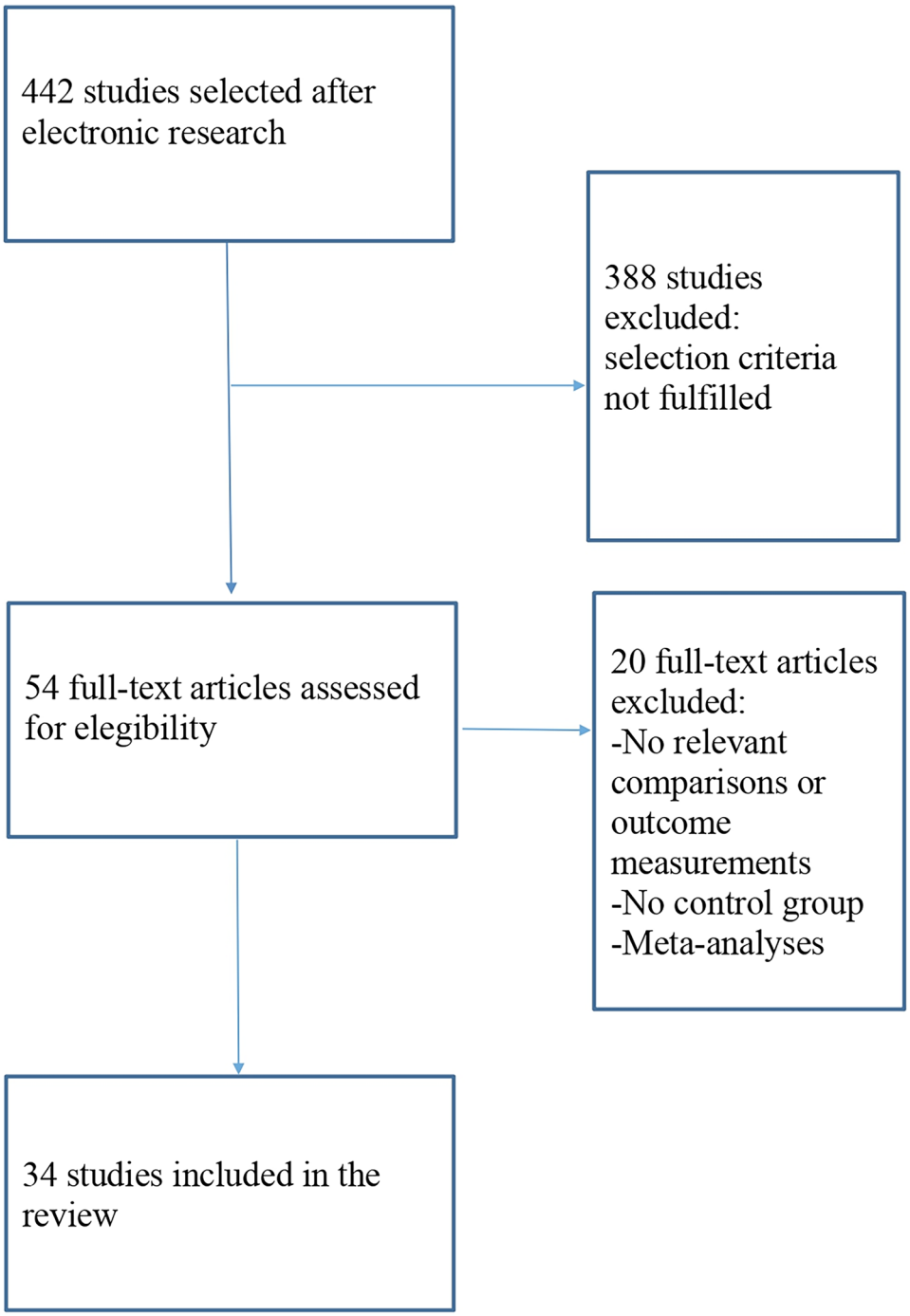

Fig. 1 Flow diagram of study identification and selection

Surgical Treatment Studies

Eleven studies evaluated the reproductive outcome of women with adenomyosis who had previously undergone conservative surgical treatment [17–20, 34–40]. Six studies were retrospective [17–19, 34, 38, 39], and five were prospective [20, 35–37, 40].

Ten studies were surgical series, without a control group of women not undergoing surgery [17–20, 35–40]. In three of these ten studies, surgical treatment was followed by either 3 months [19] or 6 months of GnRH agonist treatment [36, 38]. The remaining study compared surgical treatment with a 6-month medical treatment with GnRH agonists [34].

Four studies only included naturally conceived pregnancies [20, 34, 36, 37], while seven studies included both pregnancies from natural conception and IVF [17–19, 35, 38–40].

Five studies included both women with focal and diffuse adenomyosis [17–19, 37, 40], three studies included women with adenomyoma only [34, 36, 39], while three further studies included women with diffuse adenomyosis only [20, 35, 38]. In one study, all enrolled women had both adenomyosis and endometriosis [17].

Surgery was performed at laparotomy in seven studies [20, 34–38, 40] and at laparoscopy in two studies [17, 39], while in two studies, focal adenomyosis was treated at laparoscopy and diffuse adenomyosis at laparotomy [18, 19]. Surgical complications were reported in four studies. Two groups of authors described radical adenomyomectomy using a triple-flap technique [20, 35], and three performed a radical excision of adenomyosis leaving a 1-cm margin of tissue above the endometrium and a 1-cm margin of tissue below the serosal surface [18, 20, 35].

The weight of the removed lesions was specified in seven studies [18–20, 35, 36, 38, 39], and the size of the removed lesions was specified in three studies [19, 34, 37]. Eight studies evaluated the mode of delivery [18–20, 34, 35, 38–40]. Peripartum complications were reported in six studies [17, 18, 34, 36, 39, 40].

Outcomes

Implantation Rate

In ART studies, implantation rate was defined as the number of gestational sacs detected by the means of TVUS divided by the number of transferred embryos [5, 7, 9••, 11, 12••, 14, 23, 26, 29, 30, 33].

Clinical Pregnancy Rate

Clinical pregnancy rate was defined as clinical pregnancies/cycles in all ART studies. In the studies analyzing surgical treatment, clinical pregnancy rate was defined as clinical pregnancies/patients. Clinical pregnancy was defined as the detection of an intrauterine gestational sac by the means of TVUS [5–8, 10, 11, 29, 30] or as the ultrasonographic evidence of an embryo with a heartbeat either 4 weeks [16, 25], 5 weeks [12••], 6 weeks [15, 18, 26, 32, 33], 7 weeks [23, 28], 8 weeks [9••, 14, 27], or 12 weeks [17, 39] after embryo transfer.

Miscarriage Rate

Miscarriage was defined as the loss of a clinical pregnancy before 12 weeks [8, 14, 23, 26], 20 weeks [10, 16, 40], 22 weeks [6], 24 weeks [30], or 28 weeks [9••, 38] or regardless of gestational age [7, 10, 12••, 24, 25, 32, 34–36, 39]. Thalluri and Tremellen also included ectopic pregnancies [27]. One study defined miscarriage as the loss of a clinical pregnancy before 24 weeks, distinguishing between early miscarriage when it occurred before 12 weeks and late miscarriage when it occurred between 12 and 24 weeks [5]; similarly, Lan et al. defined early miscarriage as that occurring before 12 weeks and late miscarriage as that occurring before 24 weeks [11]. One study defined miscarriage as the ultrasonographic detection of an intrauterine gestational sac in the absence of fetal heartbeat [15].

Live Birth Rate

Live birth rate was defined as the delivery of an alive fetus/clinical pregnancy following 20 weeks [23], 22 weeks [6], 24 weeks [5], and 26 weeks of gestation [16] or regardless of gestational age [7, 8, 9••, 10, 11, 12••, 15, 24, 25, 27, 29–32, 34–36]. Four studies defined an ongoing pregnancy as a clinical pregnancy continuing past 12 weeks of gestation [14, 26, 28, 37]. One study evaluated delivery rate [30].

Among the studies analyzing ART results, only one reported mode of delivery and obstetric outcomes [7]. Conversely, of the 11 surgical studies, eight reported mode of delivery [18–20, 34, 35, 38–40], three reported abnormal placentation [17, 34, 39], and one reported uterine rupture during pregnancy [40].

Results

ART Studies

A total of 3791 women with adenomyosis and 6841 without adenomyosis were included. The findings of studies including women who conceived by means of ART are reported in Table 1. Mean (± SD) age was 36.3 ± 1.49 in women with adenomyosis and 33.5 ± 1 in those without adenomyosis.

Implantation Rate

Thirteen out of 23 studies evaluated this outcome. Overall, mean (± SD) implantation rate was 30.0% ± 7.5% in women with adenomyosis and 31.6% ± 12.1% in women without adenomyosis.

Among studies comparing women with adenomyosis and patients without adenomyosis, two out of six described a reduced implantation rate in the former group [9••, 26]. In particular, Salim et al. observed a significantly lower implantation rate in adenomyosis vs controls (18.8% vs 29.4%) [26]; similarly, Hou et al. found a significantly lower implantation rate when comparing patients with adenomyosis undergoing ultra-long or long GnRH agonist protocols versus controls (43.5% and 36.9% vs 49.5%) [9••]. No difference in implantation rate was observed between adenomyosis and

Table 1 Reproductive outcome in women with and without adenomyosis who underwent ART

Author, year	Study design	Diagnostic criteria	GnRH-a pre-treatment	Group 1	Group 2	Group 3	Adenomyosis type	Associated endometriosis % (*n*)
Costello et al. 2011 [23]	Retrospective study	TVUS before IVF cycle	/	Infertile patients with adenomyosis 18.4 (37/201), 37 cycles	Control group: infertile patients 81.6 (164/201), 164 cycles	/	nr	13.5 (5/37) vs 9.8 (16/164)
Martinez Conejero et al. 2011 [24]	Retrospective study	TVUS before IVF cycle	/	Group A: patients with adenomyosis 34.3 (152/443), 328 OD cycles	Group B: patients with adenomyosis and endometriosis 32.5 (144/443), 242 OD cycles	Group C: control group 33.2 (147/443), 331 OD cycles	nr	Group A 15.1 (23/152), Group B 100 (144/144)
Youm et al. 2011 [25]	Retrospective case–control	TVUS before IVF cycle	/	Group A: myometrial thickness < 2.00 cm: 73.1 (302/413), 397 cycles	Group B: myometrial thickness 2.00–2.49 cm: 15.3 (63/413), 81 cycles	Group C: myometrial thickness ≥ 2.5 cm: 11.6 (48/413), 73 cycles	nr	nr
	Subgroup analysis		/	Group B1: myometrial thickness 2.00–2.49 cm, without sonographic criteria suggestive for adenomyosis, 52 cycles	Group B2: myometrial thickness 2.00–2.49 cm with sonographic criteria suggestive for adenomyosis (myometrial striation, heterogeneous myometrium, myometrial cysts, or poor definition of the endometrial–myometrial junction), 29 cycles	/	nr	nr
Salim et al. 2012 [26]	Prospective study	TVUS before IVF cycle	/	Infertile patients with adenomyosis 7.0 (19/275)	Control group: infertile patients 93.0 (256/275)	/	nr	nr
Thalluri and Tremellen 2012 [27]	Retrospective study	TVUS before IVF cycle	/	Infertile patients with adenomyosis 17.8 (38/213)	Control group: infertile patients 82.2 (175/213)	/	nr	nr

Table 1 (continued)

Author, year	Study design	Diagnostic criteria	GnRH-a pre-treatment	Group 1	Group 2	Group 3	Adenomyosis type	Associated endometriosis % (*n*)
Niu et al. 2013 [28]	Retrospective study	TVUS before IVF cycle	GnRH agonist pre-treatment in group 1	Patients with adenomyosis, GnRH agonist + HRT protocol 57.2 (194/339)	Patients with adenomyosis, only HRT protocol 42.8 (145/339)	/	Adenomyoma 24.2 (82/339), 5–14 mm	nr
Benaglia et al. 2014 [29]	Prospective study	TVUS before IVF cycle	/	Asymptomatic patients with adenomyosis 50 (49/98)	Control group: Infertile patients 50 (49/98)	/	Focal adenomyosis in 49.0 (24/49) of patients Diffuse adenomyosis in 51.0 (25/49) of patients	nr
	Subgroup analysis		/	Patients with focal adenomyosis 49 (24/49)	Patients with diffuse adenomyosis 51 (25/49)	/	nr	nr
Yan et al. 2014 [30]	Retrospective study	TVUS before IVF cycle and clinical symptoms	/	Patients with adenomyosis 50 (77/154)	Control group 50 (77/154)	/	nr	27.3 (21/77) vs 14.3 (11/77)
Park et al. 2016 [31]	Retrospective study	TVUS before IVF cycle	GnRH agonist pre-treatment (3.75 mg monthly 2–3 months) in group 2 and 3	Group A: patients with adenomyosis, fresh ET 48.1 (116/241), 147 ET cycles	Group B: patients with adenomyosis, fresh ET with GnRH agonist pre-treatment 36.1 (87/241), 105 ET cycles	Group C: patients with adenomyosis, FET with GnRH agonist pre-treatment 15.8 (38/241), 43 FET cycles	nr	nr
	Subgroup analysis		/		Group B: patients with focal adenomyosis, fresh ET with GnRH agonist pre-treatment: 53, 70 cycles	Group C: patients with focal adenomyosis, FET with GnRH agonist pre-treatment: 22, 23 cycles	nr	nr

Table 1 (continued)

Author, year	Study design	Diagnostic criteria	GnRH-a pre-treatment	Group 1	Group 2	Group 3	Adenomyosis type	Associated endometriosis % (*n*)
	Subgroup analysis		/		Group B: patients with diffuse adenomyosis, fresh ET with GnRH agonist pre-treatment: 25, 35 cycles	Group C: patients with diffuse adenomyosis, FET with GnRH agonist pre-treatment 16, 20 cycles	nr	nr
	Subgroup analysis		/		Group C: patients with focal adenomyosis, fresh ET with GnRH agonist pre-treatment: 22, 23 cycles	Group C: patients with diffuse adenomyosis, FET with GnRH agonist pre-treatment: 16, 20 cycles	nr	nr
Mavrelos et al. 2017 [32]	Prospective multicentric study	TVUS 3D pre embryo transfer	/	Infertile patients with adenomyosis 19.2 (72/375)	Control group: infertile patients 80.8 (303/375)	/	nr	nr
Sharma et al. 2018 [16]	Retrospective study	TVUS 2D before pregnancy	GnRH agonist pre-treatment (3 months) in all the patients	Group B: patients with endometriosis and adenomyosis 9.1 (88/973)	Group A: patients with endometriosis 36.5 (355/973)	Group T: patients with tubal infertility 47.9 (466/973)	nr	Group A: $N=355$ Group B: $N=88$
	Retrospective study		/	Group C: patients with adenomyosis 6.6 (64/973)	Group A: patients with endometriosis 36.5 (355/973)	Group T: tubal infertility patients 47.9 (466/973)	nr	Group A: $N=355$
Stanekova et al. 2018 [15]	Retrospective study	TVUS/MRI before IVF cycle	Ultra-long GnRH agonist treatment in part of adenomyosis group	Patients with adenomyosis 19.9 (34/171) 79.4% received ultra-long GnRH agonist pre-treatment (4–12 weeks)	Control group: infertile patients 80.1 (137/171), 68.6 (94/171) were naturally ovulatory	/	nr	23.5 (8/34) vs 2.2 (3/137)
	Subgroup analysis		/	Patients with adenomyosis not pre-treated with GnRH agonist	Patients with adenomyosis pre-treated with GnRH agonist	/	nr	nr

Table 1 (continued)

Author, year	Study design	Diagnostic criteria	GnRH-a pre-treatment	Group 1	Group 2	Group 3	Adenomyosis type	Associated endometriosis % (*n*)
Liang et al. 2019 [14]	Retrospective study	TVUS and MRI before IVF cycle	52-mg 20-mg/d LNG-IUD for 3 months before FET	Patients with adenomyosis, pre-treated with LNG-IUD, 37.4 (134/358), 134 cycles	Patients with adenomyosis, not pre-treated 62.6 (224/358), 224 cycles	/	nr	nr
Chen et al. 2020 [8]	Retrospective study	TVUS before IVF cycle	GnRH agonist pre-treatment in group 2	Patients with adenomyosis, received long GnRH agonist protocol 74.4 (140/188), 162 cycles and fresh embryo transfer	Patients with adenomyosis, received long GnRH agonist protocol and GnRH agonist pre-treatment, 25.5(48/188), 52 cycles and fresh embryo transfer	/	nr	38.9 (63/162) vs 46.2 (24/52)
Hou et al. 2020 [9••]	Prospective cohort study	TVUS and Clinical signs/ symptoms before pregnancy	/	Group A: patients with adenomyosis, Ultra-long GnRH agonist treatment (3.75 mg monthly for at least 3 months) 9.2 (362/3960)	Group B: patients with adenomyosis, long GnRH agonist treatment (0.1 mg daily for 10 days and then 0.05 mg until HCG injection) 3.2(127/3960)	Group C: patients with tubal factor, long GnRH agonist treatment (0.1 mg daily for 10 days and then 0.05 mg till HCG injection) 87.6 (3471/3960)	nr	nr
Neal et al. 2020 [10]	Prospective study	TVUS 3D pre embryo transfer	/	Infertile patients with adenomyosis, 15.3(99/648)	Control group: infertile patients 84.7(549/648)	/	nr	nr
Huang et al. 2021 [33]	Retrospective study	TVUS or MRI before IVF cycle	GnRH agonist pre-treatment (Triptorelin 3.75 mg monthly 1–4 months) in both groups: 84.3 (59/70) vs 81.8 (36/44)	Patients with adenomyosis and CA125 < 35 IU/mL before HRT, $n = 70$ cycles Group 1 + Group 2 include 84 patients	Patients with adenomyosis and CA125 > 35 IU/mL before HRT, $n = 44$ cycles	/	nr	Endometriosis patients were excluded

Table 1 (continued)

Author, year	Study design	Diagnostic criteria	GnRH-a pre-treatment	Group 1	Group 2	Group 3	Adenomyosis type	Associated endometriosis % (*n*)
	Subgroup analysis		Pre-treatment with GnRH agonist	Patients with adenomyosis and CA125 < 35 U/mL, pre-treated with GnRH agonist before HRT, n.59 FET cycles	Patients with adenomyosis and CA125 > 35 U/mL, without pre-treatment, n.36 FET cycles	/	nr	nr
Iwasawa et al. 2021 [7]	Retrospective study, multicentric	MRI before IVF cycle	GnRH before ET in 20/40 advanced group 1/9 extrinsic group 0/3 intrinsic group	Infertile patients – with advanced adenomyosis (invades the full thickness of the uterine myometrium) 76.9(40/52), 100 cycles	Infertile patients – with extrinsic adenomyosis (localized on the serosal side) 17.3 (9/52), 27 cycles	Infertile patients—with intrinsic adenomyosis (localized on the endometrial side of the myometrium) 5.8 (3/52) 9 cycles	nr	60% advanced group; 44% extrinsic group; 0% intrinsic group
Lan et al. 2021 [11]	Retrospective study	TVUS/MRI before IVF cycle	/	Patients with adenomyosis ultra-long GnRH-a protocol (3.75 mg monthly for 2–4 months, ovarian stimulation started after 28 days), 64.6 (212/328), 237 cycles	Patients with adenomyosis, long GnRH-a protocol (single dose 0.93–1.87 mg at 18th or 20th day, ovarian stimulation started after 14 days), 35.4 (116 /328), 134 cycles	/	nr	Associated endometrioma: ultra-long GnRH a group 19.8 (47/237) Long GnRHa group 9.0 (12/134)
	Subgroup analysis			Patients with diffuse adenomyosis, ultra-long GnRH-a protocol, $N = 152$, 188 cycles	Patients with diffuse adenomyosis, long GnRH-a protocol, $N = 58$, 105 cycles	/	nr	nr
	Subgroup analysis			Patients with focal adenomyosis, ultra-long GnRH-a protocol, $N = 38$, 49 cycles	Patients with focal adenomyosis Long GnRH-a protocol $N = 21$, 29 cycles	/	nr	nr

Table 1 (continued)

Author, year	Study design	Diagnostic criteria	GnRH-a pre-treatment	Group 1	Group 2	Group 3	Adenomyosis type	Associated endometriosis % (*n*)
Li M et al. 2021 [6]	Retrospective study	TVUS before IVF cycle	GnRH-a pre-treatment in the case group 1–3 months	Patients with focal adenomyosis, received hormone replacement cycle + GnRH-a 46.9 (160 /341)	Patients with focal adenomyosis, received hormone replacement cycle 53.1 (181/341)	/	nr	nr
Li X et al. 2021 [5]	Retrospective study	TVUS before IVF cycle	GnRH agonist pre-treatment in both groups 2–7 months	Group A: patients with focal adenomyosis, uterine volume ≤ 98.81 cm3 52.5 (83/158)	Group B: patients with focal adenomyosis, uterine volume > 98.81 cm3 47.5 (75/158)	/	Group A: diffuse adenomyosis 73.5 (61/83) and focal adenomyosis 26.5 (22(83)% Group B: diffuse adenomyosis 77.3 (58/75), focal adenomyosis 22.7 (17/75	24.1% vs 25.3%
Zhang J et al. 2021 [12••]	Retrospective study	TVUS before IVF cycle	GnRH-a pre-treatment in both groups (3.75 mg IM monthly for 1–6 months)	Patients with focal adenomyosis, pre-treated with GnRH-a 19.7 (51/259)	Patients with endometriosis, pre-treated with GnRH-a 80.3 (208/259) Matched at ratio 1:4 according to age	/	nr	Group 2: 100 (208/208) endometriosis patients
Zhang X et al. 2021 [13]	Retrospective study	TVUS before IVF cycle	/	Patients with focal adenomyosis and tubal infertility 50 (180/360)	Control group: patients with tubal infertility 50 (180/360)	/	nr	nr

Table 1 (continued)

Author, year	Age, mean, or median (years) ± SD	ART type	Protocol	ET	Implantation rate % (*n*)	Clinical pregnancy/cycle % (*n*)	Miscarriage/clinical pregnancy % (*n*)	Live birth/cycle % (*n*)
Costello et al. 2011 [23]	39.0 (27–42) vs 34.6 (18–42)	IVF/ICSI	Long down regulation protocol GnRH agonist	Included only 1st fresh cycle per patient N. of transferred embryos 1 (0–3) Cleavage stage 100 (31/31) vs 98.6 (137/139)	28.3 (15/53) vs 31.6 (65/206)	35.1 (13/37) vs 31.1 (51/164)	15.4 (2/13) vs 27.1 (16/59)	29.7 (11/37) vs 26.1 (42/161)
Martinez Conejero et al. 2011 [24]	40.5 (39.8–41.3) vs 37.3 (36.6–37.9) vs 40.9 (40.3–41.6)	IVF + OD	OD protocol	N. of transferred embryos 1.97 vs 1.93 vs 1.90	A vs B vs C 29.6% vs 33.3% vs 30.8%	A vs B vs C 40 (131/328) vs 44.2 (107/242) vs 44.4 (147/331)	A vs B vs C 13.1 (43/328) vs 6.1 (15/242) vs 7.2 (24/331)	A vs B vs C 26.8 (88/328) vs 38.0 (92/242) vs 37.1 (123/331)[a]
Youm et al. 2011 [25]	33.0 ± 3.7 vs 33.7 ± 3.7 vs 33.6 ± 3.7	IVF-ET	GnRH agonist	N. of transferred embryos 3.1 ± 0.8 vs 3.2 ± 0.8 vs 3.1 ± 0.8	A vs B vs C 22.8 (264/1158) vs 21.9 (55/251) vs 12.3 (28/228)	A vs B vs C 56.4 (224/397) vs 53.1 (43/81) vs 31.5 (23/73)	A vs B vs C 12.9 (29/224) vs 20.9 (9/43) vs 52.2 (12/23)	A vs B vs C 46.9 (186/397) vs 40.7 (33/81) vs 15.1 (11/73)
	nr	IVF-ET	nr	nr	B1 vs B2 27.2 (44/162) vs 12.4 (11/89)	B1 vs B2 63.5 (33/52) vs 34.5 (10/29)	B1 vs B2 12.1 (4/33) vs 50.0 (5/10)	B1 vs B2 53.8 (28/52) vs 17.2 (5/29)
Salim et al. 2012 [26]	34.0 ± 3.67 vs 34.6 ± 4.06	IVF/ICSI	GnRH agonist	N. of transferred embryos: 2 (1–3) vs 2 (1–2)	18.8 (6/32) vs 29.4 (123/419)[b]	22.2 (4/18) vs 47.2 (108/229)[b]	50.0 (2/4) vs 2.8 (3/108)	11.1 (2/18) vs 45.9 (105/229)
Thalluri and Tremellen, 2012 [27]	35(32.7–37.3) vs 33(30–36)	IVF/ICSI	GnRH antagonist	Included only 1st cycle per patient	nr	23.6 (9/38) vs 44.6 (78/175)	25 (3/12) vs 10.3 (9/87)[d]	nr
Niu et al. 2013 [28]	32.11 ± 4.02 vs 31.52 ± 4.03	IVF/ICSI	Long GnRH agonist	FET N.of embryos transferred 1.96 ± 0.4 vs 1.94 ± 0.37	32.5 (127) vs 16.1 (45) [e]	51.3 (100) vs 24.8 (36/145) [e]	nr	48.9 (90) vs 21.4 (31/145) [e,f]
Benaglia et al. 2014 [29]	35 ± 4 vs 35 ± 4	IVF/ICSI	Long GnRH protocol 53% vs 53% GnRH antagonist 22% vs 29% Short GnRH protocol 22% vs 16% Others 2% vs 2%	Fresh ET N. of embryos transferred 1.55 vs 1.55	32 (24/76) vs 21 (16/76)	43 (21/49) vs 29 (14/49)	19 (4/21) vs 36 (5/14)	35 (17/49) vs 18 (9/49)
	nr	IVF/ICSI	nr	nr	32 (12/38) vs 32 (12/38)	46 (11/24) vs 40 (10/25)	nr	33 (8/24) vs 36 (9/25)

Table 1 (continued)

Author, year	Age, mean, or median (years) ± SD	ART type	Protocol	ET	Implantation rate % (*n*)	Clinical pregnancy/cycle % (*n*)	Miscarriage/clinical pregnancy % (*n*)	Live birth/cycle % (*n*)
Yan et al. 2014 [30]	34.18 ± 4.19 vs 34.23 ± 4.17	IVF/ICSI	Short GnRH agonist 22% vs 23.4% Long GnRH agonist 36.4% vs 38.9% Ultra-long GnRH agonists 37.7% vs 31.2% Mild stimulation 2.6% vs 3.9% Other 1.3% vs 2.6%	Fresh ET Considered only 1 embryo transfer per each patient N.of embryos transferred 1.93 vs 1.96	nr	36.4 (28/77) vs 45.5 (35/77) [g]	50 (19/38) vs 36.9 (17/46)	24.8 (19/77) vs 33.3 (29/77) [a]
Park et al. 2016 [31]	36.1 ± 3.3 vs 35.2 ± 3.5 vs 34.9 ± 4.0	IVF/ICSI	GnRH agonist	Fresh ET and FET N.of embryos transferred 2.7 ± 1.1 vs 2.9 ± 1.1 vs 3.4 ± 0.6	nr	A vs B vs C 25.2 (37/147) vs 30.5 (32/105) vs 39.5 (17/43)	A vs B vs C 6.1 (9/147) vs 9.5 (10/105) vs 13.9 (6/43)	nr
	nr	IVF/ICSI	nr	nr	nr	Focal adenomyosis B vs C 32.9 (23/70) vs 43.5 (10/23)	Focal adenomyosis B vs C 7.1 (5/70) vs 13 (3/23)	nr
	nr	IVF/ICSI	nr	nr	nr	Diffuse adenomyosis B vs C 25.7 (9/35) vs 35 (7/20)	Diffuse adenomyosis B vs C 14.3 (5/35) vs 15 (3/20)	nr
	nr	IVF/ICSI	nr	nr	nr	Group C Focal vs diffuse 43.5 (10/23) vs 35.0 (7/20)	Group C Focal vs diffuse 13 (3/23) vs 15 (3/20)	nr
Mavrelos et al. 2017 [32]	36.0 [IQR 33.00–38.75] vs 34.0 [IQR 31.0–37.0]	IVF-ET	Long agonist, long agonist with discontinuation of GnRH agonist, antagonist	nr	nr	29.2 (21/72) vs 42.6 (129/303)	4.8 (1/21) vs 16.3 (21/129)	nr
Sharma et al. 2018 [16]	Group B: 32.1 ± 3.0 vs Group A: 32.7 ± 2.5 Group T: 33.0 ± 3.4	IVFI/ICSI	Ultra-long GnRH agonist protocol	nr	nr	B vs A 22.7 (20/88) vs 36.6 (130/355)	B vs A 35 (7/20) vs 14.6 (19/130)	B vs A 11.4 (10/88) vs 26.5 (94/355)

Table 1 (continued)

Author, year	Age, mean, or median (years) ± SD	ART type	Protocol	ET	Implantation rate % (*n*)	Clinical pregnancy/cycle % (*n*)	Miscarriage/clinical pregnancy % (*n*)	Live birth/cycle % (*n*)
	Group C 32.9 ± 3.0 Group A 32.7 ± 2.5 Group T 33.0 ± 3.4	IVFI/ICSI	nr	nr	nr	C vs A 23.4 (15/64) vs 36.6 (130/355)	C vs A 40 (6/15) vs 14.6 (19/130)	C vs A 12.5 (8/64) vs 26.5 (94/355)
Stanekova et al. 2018 [15]	37.0 ± 4.0 vs 35.9 ± 4.6	IVF/ICSI	nr	Genetically screened frozen–thawed embryo Single FET	NR because only patients with evidence of biochemical pregnancy were included	55.9 (19/34) vs 84.6 (116/137)	53.0 (18/34) vs 19.7 (27/137) [g] Biochemical miscarriage 44.1 (15/34) vs 15.3 (21/137)	47 (16/34) vs 80 (110/137)
	nr	IVF/ICSI	nr	nr	nr	nr	82.4% vs 35.7%	nr
Liang et al. 2019 [14]	36.1 ± 4.0 vs 36.2 ± 4.7	IVF	None	N = 1 FET cycle for each patient N. of transferred embryos 1.86 ± 0.35 vs 1.79 ± 0.44	32.1 (75/234) vs 22.1 (89/403)	44 (59/134) vs 33.5 (75/224),	3.4 (2/59) vs 9.3 (7/75)	41.8 (56/134) vs 29.5 (66/224)
Chen et al. 2020 [8]	33.5 vs 33.5	IVF/ICSI	Long GnRH agonist protocol	Fresh ET cycles 37.7% vs 21.2% Blastocyst or cleavage stage embryo N. of transferred embryos: 2 (2–3)	nr	42.6 (69/162) vs 30.8 (16/52)	11.6 (8/162) vs 31.3 (5/52)	37.7 (61/162) vs 21.2 (11/52)
Hou et al. 2020 [9••]	31.9 vs 31.8 vs 31.6	IVF/ICSI	Long or Ultra-long GnRH agonist	Cleavage stage embryo N. of transferred embryos: 1 or 2	C vs A 49.5 vs 43.5 C vs B 49.5 vs 36.9	C vs A 68.4 vs 63.8 C vs B 68.4 vs 50.5 A vs B 63.8 vs 50.5	C vs A 10.4 vs 17.4 C vs B 10.4 vs 25.5	C vs A 58.5 vs 52.4 C vs B 58.5 vs 37.6 A vs B, 52.4 vs 37.6
Neal et al. 2020 [10]	37.1 ± 5.2 vs 35.9 ± 4.6	IVF/ICSI	GnRH agonist 12.1 (12/99) vs 5.1 (28/549)	FET cycles Single thawed euploid blastocyst	nr	80.0 (76/95) vs 75.0 (407/543)[h]	10.5 (10/95) vs 7.7 (42/543)	69.5 (66/95) vs 66.5 (361/543)
Huang et al. 2021 [33]	32.77 ± 3.75 vs 32.0 ± 3.97	IVF/ICSI	nr	FET cycles Blastocyst or cleavage stage embryo N.of transferred embryos: 1.70 ± 0.60 vs 1.89 ± 0.62	28.4 (33/116) vs 22.9 (19/83)	35.7 (25/70) vs 31.8 (14/44)	20 (5/70) vs 35.7 (5/44)	28.6 (20/70) vs 20.5 (9/44)
	nr	IVF/ICSI	nr	nr	nr	32.2% vs 32.3%	26.3% vs 33.3%	23.7% vs 22.2%

Table 1 (continued)

Author, year	Age, mean, or median (years) ± SD	ART type	Protocol	ET	Implantation rate % (*n*)	Clinical pregnancy/cycle % (*n*)	Miscarriage/clinical pregnancy % (*n*)	Live birth/cycle % (*n*)
Iwasawa et al. 2021 [7]	36 (26–41) vs 37 (30–39) vs 35 (31–36)	IVF/ICSI	Short/long/ultra-long GnRH agonist protocol, GnRH antagonist	Fresh ET and FET N.of transferred embryos: 1 (1–2)	nr	Advanced 25 (25/100), extrinsic 33.3 (9/27), intrinsic 22.2 (2/9) [b]	Advanced 64 (16/25) Extrinsic 33.3 (3/9) Intrinsic 50 (1/2)	Advanced 9 (9/100), Extrinsic 22.2 (6/27), Intrinsic 11.1 (1/9) [b]
Lan et al. 2021 [11]	33.55 ± 4.12 vs 33.99 ± 4.08,	IVF/ICSI	Long or ultra-long GnRH agonist protocol	Fresh ET Blastocyst or cleavage stage embryo N.of transferred embryos: 2.05 ± 0.57 vs 2.05 ± 0.55	36.2 (141/389) vs 30.2 (49/162)	52.6 (100/190) vs 43 (34/79)	Early miscarriage (< 12w) 12.0 (12/100) vs 26.5 (9/34) Late miscarriage < 24 w	41.6 (79/190) vs 30.4 (24/79)
	nr	IVF/ICSI	nr	nr	nr	55.3 (84/152), vs 37.9 (22/58)	11.9 (10/84), vs 27.3 (6/22)	43.4 (66/152) vs 25.9 (15/58)
	nr	IVF/ICSI	nr	nr	nr	42.1 (16/38) vs 57.1 (12/21)	12.5 (2/16) vs 25.0 (3/12)	34.2 (13/38) vs 42.9 (9/21)
Li M et al. 2021 [6]	34.56 ± 4.49 vs 35.25 ± 4.95	IVF/ICSI	Short/long/ultra-long GnRH agonist protocol, GnRH antagonist	FET cycles Blastocyst or cleavage stage embryo N.of transferred embryos: ≤ 2	nr	40.6 (65/160) vs 42.5 (77/181)	41.5 (27/65) vs 44.2 (34/77)	23.7 (38/160) vs 23.7 (43/181)
Li X et al. 2021 [5]	33.84 ± 3.23 vs 33.87 ± 3.86	IVF	Long GnRH agonist protocol	FET cycles Only 1st blastocyst transfer cycle N.of transferred embryos 1.25 ± 0.44	43.3 (45/104) vs 40.0 (38/95)	51.8 (43/83) vs 52.0 (39/75)	16.3 (7/43) vs 51.23 (20/39) Early (< 12w) 13.9 (6/43) vs 38.5 (15/39) Late (12–24w) 2.33 (1/43) vs 12.8 (5/39)	43.4 (36/83) vs 25.3 (19/75)

Table 1 (continued)

Author, year	Age, mean, or median (years) ± SD	ART type	Protocol	ET	Implantation rate % (*n*)	Clinical pregnancy/cycle % (*n*)	Miscarriage/clinical pregnancy % (*n*)	Live birth/cycle % (*n*)
Zhang J et al. 2021 [12••]	32.25 ± 3.76 vs 32.15 ± 3.69	IVF/ICSI	Long GnRH agonist protocol	ET N.of transferred embryos:1.84 ± 0.37 vs 1.84 ± 0.37	31.9 (30/94) vs 46.7 (179/383)	47.1 (24/51) vs 64.4 (134/208)	33.3 (8/24) vs 13.4 (18/134)	31.4 (16/51) vs 54.8 (114/208)
Zhang X et al. 2021 [13]	34.0 ± 4.0 vs 33.7 ± 3.6	IVF/ICSI	Short or long GnRH agonist protocol, GnRH antagonist	FET Blastocyst or cleavage stage embryo	28.4 (99/180) vs 31.7 (112/180)	42.2 (76/180) vs 42.8 (77/180)	Early miscarriage 13.3 (24/180) vs 5.6 (10/180) Late miscarriage, 5.0% vs 2.2%	22.8 (41/180) vs 33.3 (60/180)

ART assisted reproductive technology, *GnRH* gonadotropin-releasing hormone, *ET* embryo transfer, *TVUS* transvaginal ultrasound, *IVF* in vitro fertilization, *nr* not reported, *ICSI* intracytoplasmic sperm injection, *OD* oocyte donation, *HRT* hormone replacement therapy, *FET* frozen-thawed embryo transfer cycle, *MRI* magnetic resonance imaging, *LNG-IUD* levonorgestrel-releasing intrauterine device, *HCG* human chorionic gonadotropin

Numbers are expressed as percentage (absolute value) or median ± SD or median [interquartile range] or absolute value

[a]Term pregnancy rate

[b]Clinical pregnancy/embryo transfer; implantation/n. embryos transferred

[c]Ongoing pregnancy/ongoing clinical pregnancies

[d]Comprehensive of miscarriage + ectopic pregnancies

[e]Some data are missing

[f]Clinical pregnancy continuing past 12 weeks of gestation

[g]Including miscarriage at a biochemical + clinical stage

[h]Four cases underwent termination of pregnancy for fetal anomaly

controls by Costello et al. (28.3% vs 31.6%) [23], Zhang et al. (28.4% vs 31.7%) [13], and Benaglia et al. (32% vs 21%) [29]. Martinez-Conejero et al. found no significant difference in implantation rate when comparing women with adenomyosis both with controls (29.6% vs 30.8%) and with women with endometriosis plus adenomyosis (29.6% vs 33.3%) [24].

Among women with adenomyosis, a significantly higher implantation rate was observed by Niu et al. in those pre-treated as compared to those not pre-treated with GnRH agonists (32.5% vs 16.1%) [28]. Liang et al. reported a significantly higher implantation rate among women with adenomyosis pre-treated with LNG-IUD, compared to those not pre-treated (32.1% vs 22.1%) [14].

Among women with adenomyosis undergoing an ultra-long vs long protocol with GnRH agonists, Lan et al. observed no difference in implantation rate between the two groups (36.2% vs 30.2%) [11].

Huang et al. found no significant difference in implantation rates in women with adenomyosis when comparing those with levels of CA125 < 35 IU/ml and those with levels > 35 IU/mL (28.4% vs 22.9%) [33]. In Youm et al.'s study, a significantly lower implantation rate was observed in women with a myometrial thickness > 2.49 cm, compared to those whose myometrial thickness was < 2.0 cm and 2.0–2.49 cm, respectively (12.3% vs 22.8% and 12.3% vs 21.9%). Among women whose myometrial thickness ranged between 2.0 and 2.49 cm, the implantation rate was significantly higher when sonographic criteria for adenomyosis were absent rather than present (27.2% vs 12.4%) [25]. Analyzing women with adenomyosis pre-treated with GnRH agonists, Li et al. found no difference in implantation rates between those with a uterine volume < 98.81 cc and those with a uterine volume > 98.81 cc (43.3% vs 40%) [5]. Benaglia et al. found no difference in implantation rates when comparing focal and diffuse adenomyosis (32% vs 32%) [29].

Comparing women with adenomyosis to those with endometriosis, both pre-treated with GnRH agonists, Zhang et al. found a significantly lower implantation rate in the former group (31.9% vs 46.7%) [12••].

Clinical Pregnancy Rate

All 23 ART studies evaluated this outcome. Overall, mean (± SD) clinical pregnancy rate/cycle was 39.4% ± 12.8% in women with adenomyosis and 49.8% ± 16.5% in women without adenomyosis.

Among studies comparing patients with adenomyosis and controls, six out of 12 described a reduced pregnancy rate in the former group [9••, 15, 16, 26, 27, 32]. In particular, a significantly lower pregnancy rate in women with adenomyosis vs controls was observed by Salim et al. (22.2% vs 47.2%) [26], Thalluri and Tremellen (23.6% vs 44.6%) [27], Mavrelos et al. (29.2% vs 42.6%) [32], and Stanekova et al. (55.9% vs 84.6%) [15]. A significantly lower pregnancy rate compared to controls was observed by Hou et al. in women with adenomyosis undergoing an ultra-long (63.8% vs 68.4%) or a long GnRH agonist protocol (50.5% vs 68.4%) [9••]. Sharma et al. reported a significantly lower pregnancy rate in women with both adenomyosis and endometriosis compared to patients with tubal infertility (controls versus adenomyosis plus endometriosis: 34.5% vs 22.7%), as in both the adenomyosis group and the adenomyosis plus endometriosis group, compared to the endometriosis only group (23.4% vs 36.6% and 22.7% vs 36.6%). However, they did not observe a lower pregnancy rate in the adenomyosis group compared to the tubal infertility group (23.4% vs 34.5%) [16]. Conversely, no difference in pregnancy rate was observed between women with adenomyosis and controls in studies by Costello et al. (35.1% vs 31.1%) [23], Benaglia et al. (43% vs 29%) [29], Yan et al. (36.4% vs 45.5%) [30], Neal et al. (80% vs 75%) [10], and Zhang et al. (42.2% vs 42.8%) [13]. Martinez-Conejero et al. found no significant difference in pregnancy rates when comparing patients with adenomyosis versus controls (40% vs 44.4%) and versus women with endometriosis plus adenomyosis (40% vs 44.2%) [24].

Among women with adenomyosis, Niu et al. observed a significantly higher clinical pregnancy rate in those pre-treated with GnRH agonists as compared to those not pre-treated (51.3% vs 24.8%) [28], whereas no difference was observed between the two groups by Chen et al. (30.8% vs 42.6%) [8] and Li et al. (40.6% vs 42.5%) [6]. Park et al. observed no difference when comparing clinical pregnancy rate in not pre-treated fresh ET (25.2%) with both pre-treated fresh ET (30.5%) and pre-treated frozen ET (39.5%) [31]. Liang et al. found a significantly higher pregnancy rate among women with adenomyosis who were pre-treated with LNG-IUD as compared to not pre-treated women (44% vs 33.5%) [14].

Among patients with adenomyosis undergoing an ultra-long vs long protocol with GnRH agonists, a significantly higher clinical pregnancy rate for the former group was observed by Hou et al. (63.8% and 50.5%) [9••], whereas no difference was observed by Lan et al. (52.6% vs 43%) [11]. However, in Lan et al.'s study, the ultra-long protocol was associated with a significantly higher rate of clinical pregnancy in women with diffuse adenomyosis (55.5% vs 37.9%) [11].

When comparing levels of CA125 < 35 IU/ml with levels > 35 IU/mL in women with adenomyosis, Huang et al. found no significant difference in pregnancy rate (35.7% vs 31.8%). Also, no significant difference was found when comparing women who were pre-treated with GnRH agonists with those not pre-treated (32.2% vs 32.3%) [33]. In

Youm et al.'s study, a significantly lower pregnancy rate was observed in women with a myometrial thickness > 2.49 cm compared to women with myometrial thickness < 2.0 cm and 2–2.49 cm, respectively (31.5% vs 56.4% and 31.5% vs 53.1%). In women with a myometrial thickness ranging between 2.0 and 2.49 cm, the clinical pregnancy rate was significantly higher when sonographic criteria for adenomyosis were absent rather than present (63.5% vs 34.5%) [25]. When analyzing women with adenomyosis pre-treated with GnRH agonists, Li et al. described a comparable clinical pregnancy rate between those with a uterine volume < 98.81 cc and those with a uterine volume > 98.81 cc (51.8% vs 52%) [5]. Iwasawa et al. observed comparable pregnancy rates between women with advanced, extrinsic, and intrinsic adenomyosis (25% vs 33.3% vs 22.2%, respectively) [7]. Comparable pregnancy rates between women with diffuse and focal adenomyosis were observed by Benaglia et al. (46% vs 40%) [29] and Park et al. (43.5% vs 35%) [31]. In the latter study, women were pre-treated with GnRH agonists.

Comparing patients with adenomyosis to those with endometriosis, both pre-treated with GnRH agonists, Zhang et al. found a significantly lower clinical pregnancy rate in the former group (47.1% vs 64.4%) [12••].

Miscarriage Rate

Twenty-two out of 23 studies evaluated this outcome [5–8, 9••, 10, 11, 12••, 13–16, 23–27, 29–33]. Overall, the mean (± SD) miscarriage rate was 26.3% ± 16.9% in women with adenomyosis and 15.3% ± 10.6% in women without adenomyosis.

Among studies comparing women with adenomyosis with those without adenomyosis, six out of 12 described an increased miscarriage rate in the former group [9••, 13, 15, 16, 24, 26]. In particular, when comparing adenomyosis vs controls, Salim et al. observed a significantly higher miscarriage rate (50% vs 2.8%) [26], Zhang et al. reported a significantly higher rate of early miscarriage (13.3% vs 5.6%) and a comparable rate of late miscarriage (5.0% vs 2.2%) [13], while Stanekova et al. observed a significantly higher rate of early miscarriage, including miscarriage at a biochemical stage (53% vs 19.7%) [15]. A significant increase in miscarriage rate was observed by Martinez-Conejero et al. when comparing women with adenomyosis both versus controls (13.1% vs 7.2%) and versus women with endometriosis plus adenomyosis (13.1% vs 6.1%) [24]. Sharma et al. reported a significantly higher miscarriage rate in both the adenomyosis group and the adenomyosis plus endometriosis group compared to the tubal infertility group (40% vs 13% and 35% vs 13%); a higher miscarriage rate was also observed in the adenomyosis group and in the adenomyosis plus endometriosis group, compared to the endometriosis group (40% vs 14.6% and 35% vs 14.6%, respectively) [16].

A significantly higher miscarriage rate when comparing patients with adenomyosis undergoing an ultra-long or long GnRH agonist protocol and controls was observed by Hou et al. (17.4% and 25.5% vs 10.4%) [9••]. No difference in miscarriage rates between adenomyosis and controls was observed by Costello et al. (15.4% vs 27.1%) [23], Thalluri and Tremellen (25% vs 10.3%) [27], Benaglia et al. (19% vs 36%) [29], Yan et al. (50% vs 36.9%) [30], Mavrelos et al. (4.8% vs 16.3%) [32], and Neal et al. (10.5% vs 7.7%) [10].

Among women with adenomyosis, a significantly lower miscarriage rate was observed in those pre-treated as compared to those not pre-treated with GnRH agonists by Stanekova et al. (82.4% vs 35.7%) [15], whereas no difference was observed between the two groups by Chen et al. (31.3% vs 11.6%) [8], Li et al. (41.5% vs 44.2%) [6], and Huang et al. (26.3% vs 33.3%) [33]. Park et al. observed no difference comparing miscarriage rates in not pre-treated fresh ET (6.1%) vs both pre-treated fresh ET (9.5%) and pre-treated frozen ET (13.9%) [31]. Liang et al. observed a comparable miscarriage rate between patients with adenomyosis who were pre-treated with LNG-IUD and those not pre-treated (3.4% vs 9.3%) [14].

Among women with adenomyosis undergoing an ultra-long vs long protocol with GnRH agonists, a significantly lower early miscarriage rate for the former group was observed by Lan et al. (12% vs 26.5%). In the same study, the late miscarriage rate was not significantly different between the two groups (8.0% vs 2.9%) nor was it significantly different between diffuse and focal adenomyosis [11].

Analyzing women with adenomyosis, Huang et al. found no significant difference in miscarriage rates when comparing women with levels of CA125 < 35 IU/ml and those with CA125 > 35 IU/mL (20% vs 35.7%) [33]. In Youm et al.'s study, a significantly higher miscarriage rate was observed in women with a myometrial thickness > 2.49 cm, compared to women with a myometrial thickness < 2.0 cm and 2.0–2.49 cm, respectively (52.2% vs 12.9% and 52.2% vs 20.9%). Among women with a myometrial thickness ranging between 2.0 and 2.49 cm, the miscarriage rate was significantly lower when sonographic criteria for adenomyosis were absent rather than present (12.1% vs 50%) [25].

When analyzing women pre-treated with GnRH agonists, Li et al. observed a higher rate of both miscarriage and early miscarriage (< 12 weeks) in those with a bulky uterus > 98.81 cc, compared to those with a uterine volume < 98.81 cc (51.2% vs 16.3% and 38.5% vs 13.9%, respectively) [5]. Iwasawa et al. observed comparable miscarriage rates between women with advanced, extrinsic, and intrinsic adenomyosis (64% vs 33.3% vs 50%, respectively) [7]. In Park et al.'s study, among pre-treated women, miscarriage rate did not differ between those with diffuse and focal

adenomyosis (14.3% vs 15% and 7.1% vs 13%, respectively) [31].

Comparing women with adenomyosis to those with endometriosis, both pre-treated with GnRH agonists, Zhang et al. found a significantly higher miscarriage rate in the former group (33.3% vs 13.4%) [12••].

Live Birth Rate

This outcome was evaluated in 20 out of 23 studies [5–8, 9••, 10, 11, 12••, 13–16, 23–26, 28–30, 33]. Overall, the mean (± SD) live birth rate was 29.9% ± 13.7% in women with adenomyosis and 42.6% ± 18.2% in women without adenomyosis. Seven out of 10 studies comparing women with adenomyosis and women without adenomyosis described a reduced live birth rate in the former group [9••, 13, 15, 16, 24, 26, 30]. In particular, a significantly lower live birth rate in the adenomyosis vs control group was observed by Yan et al. (24.8% vs 33.3%) [30], Stanekova et al. (47% vs 80%) [15], and Zhang et al. (22.8% vs 33.3%) [13]. A significantly lower live birth rate in adenomyosis vs controls was observed by Salim et al. (11.1% vs 45.9%) [26]. A significantly lower live birth rate was observed by Hou et al. in women with adenomyosis undergoing an ultra-long (52.4% vs 58.5%) or a long GnRH agonist protocol compared to controls (37.6% vs 58.5%) [9••]. Sharma et al. reported a significantly lower live birth rate in both the adenomyosis group and in the adenomyosis plus endometriosis group, compared to the tubal infertility group (12.5% vs 27.5% and 11.4% vs 27.5%, respectively). Similar results were reported in both the adenomyosis group and the adenomyosis plus endometriosis group, compared to the endometriosis group (12.5% vs 26.5% and 11.4% vs 26.5%, respectively) [16]. A significant decrease in live birth rate was observed by Martinez-Conejero et al. when comparing women with adenomyosis with controls (26.8% vs 37.1%) and with women with endometriosis plus adenomyosis (26.8% vs 38%) [24]. No difference in live birth rate was observed between adenomyosis and controls by Costello et al. (29.7% vs 26.1%) [23], Benaglia et al. (35% vs 18%) [29], and Neal et al. (69.5% vs 66.5%) [10].

A significantly higher live birth rate was observed in women with adenomyosis who were pre-treated with GnRH agonists as compared to those not pre-treated by Niu et al. (48.9% vs 21.4%) [28], whereas no difference was observed by Li et al. (23.7% vs 23.7%) [6]. Interestingly, Chen et al. reported a higher live birth rate in women with adenomyosis not pre-treated with GnRH agonists as compared to those pre-treated (37.7% vs 21.2%) [8]. Liang et al. found a significantly higher live birth rate among women with adenomyosis pre-treated with LNG-IUD compared to not pre-treated women (41.8% vs 29.5%) [14].

Lan et al. observed no difference in live birth rate when comparing women with adenomyosis undergoing an ultra-long vs long protocol with GnRH agonists (41.6% vs 30.4%). However, the ultra-long protocol was associated with a significantly higher rate of live birth in women with diffuse adenomyosis (43.4% vs 25.9%), whereas no difference was observed in women with focal adenomyosis [11].

Huang et al. found no significant differences in live birth rate between women with serum levels of CA125 < 35 IU/ml and those with levels > 35 IU/mL (28.6% vs 20.5%). Similarly, no differences were observed when comparing women pre-treated with GnRH agonists with those not pre-treated [33]. Youm et al. observed a significantly lower live birth rate in women with myometrial thickness > 2.49 cm compared to women with a myometrial thickness < 2.0 cm and 2.0–24.9 cm, respectively (15.1% vs 46.9% and 15.1% vs 40.7%). Among women with a myometrial thickness ranging between 2.0 and 2.49 cm, live birth rate was significantly higher when sonographic criteria for adenomyosis were absent rather than present (53.8% vs 17.2%) [25].

Analyzing women with adenomyosis pre-treated with GnRH agonists, Li et al. described a higher live birth rate in those with a uterine volume < 98.81 cc compared to those with a uterine volume > 98.81 cc (43.4 vs 25.3%) [5]. Iwasawa et al. observed a comparable live birth rates between women with advanced, extrinsic, and intrinsic adenomyosis (9% vs 22.2% vs 11.1%, respectively) [7]. Benaglia et al. observed comparable live birth rates between women with diffuse versus focal adenomyosis (33% vs 36%) [29].

Comparing women with adenomyosis to those with endometriosis, both pre-treated with GnRH agonists, Zhang et al. found a significantly lower live birth rate in the former group (31.4% vs 54.8%) [12••].

Mode of Delivery and Abnormal Placentation

In a series of 16 women with adenomyosis conceiving by ART, the rate of cesarean section was 62.5%, the rate of preterm delivery was 18.8%, and the rate placenta previa was 6.2% [7].

Surgical Treatment Studies

The reproductive outcome of a total of 961 women who previously underwent surgical treatment of adenomyosis was evaluated in 11 studies [17–20, 34–40]. The findings of patients who underwent conservative surgery are reported in Table 2.

The mean weight of the removed lesions was 133.3 g ± 194.3 g [18–20, 35, 36, 38, 39].

Surgical complications included small, self-reabsorbing myometrial hematomas in 5.8% of women [35], Asherman's

Table 2 Reproductive outcome of women with and without adenomyosis who underwent conservative surgical treatment

Author, year	Study design	Diagnostic criteria	Surgery technique	Group 1	Group 2	Adenomyosis type and localization	Lesion removed weight (g) or size (cm) or volume (cm^3)	Associated endometriosis % (*n*)
Al Jama 2011 [34]	Retrospective study	TVUS and MRI	Conservative "cytoreductive" surgery: the focal adenomyotic lesions were excised, all dead spaces were obliterated with horizontal and interlocking surgical sutures. The serosa was closed with a continuous, inverting, interlocking suture	Group A: symptomatic sub-fertile patients with adenomyosis treated with GnRH agonist treatment (3.5 mg monthly for 6 months) 55 (22/40)	Group B: symptomatic sub-fertile patients with adenomyosis treated with conservative surgery and subsequent GnRH agonist treatment (3.5 mg monthly for 6 months) 45 (18/40)	Lesions were mostly in the anterio/lateral wall, while in two patients, the adenoma was located in the posterio-lateral uterine wall	Adenomyoma size: 2–4.5 cm	nr
Osada et al. 2011 [35]	Prospective case series	TVUS and MRI	Mini-LPT, radical adenomyomectomy (leaving 1 cm margin of tissue above endometrium and 1 cm margin of tissue below the serosal surface) with triple-flap without overlapping suture lines	Symptomatic patients with diffuse adenomyosis, involving more than 80% of the anterior and/or posterior wall of the uterus with an enlargement of more than 6 cm in thickness 100 (104/104)	/	Localization of adenomyoma: 36.5 (38/104) anterior wall, 42.3 (44/104) posterior wall, 21.2 (22/104) both anterior and posterior walls	Myometrium removed 292.6 g ± 254.1 g	nr
Chang et al. 2012 [36]	Prospective study	TVUS	Mini LPT, adenomyomectomy	Patients with adenomyosis, treated with conservative surgery and subsequent GnRH agonist treatment (3.75 mg monthly for 6 months) 100 (56/56)	/	Localization of adenomyoma: anterior wall 32.1 (18/56), posterior wall 53.6 (30/56), fundal 14.3 (8/56)	Adenomyoma weight: 177.6 g ± 64.0 g	nr

Table 2 (continued)

Author, year	Study design	Diagnostic criteria	Surgery technique	Group 1	Group 2	Adenomyosis type and localization	Lesion removed weight (g) or size (cm) or volume (cm^3)	Associated endometriosis % (*n*)
Dai et al. 2012 [37]	Prospective study	TVUS	LPT: excision of adenomyoma	Symptomatic patients with adenomyosis 100 (86/86)	/	Focal and diffuse adenomyosis	Median adenomyoma volume: 115cm^3	nr
Huang et al. 2012 [38]	Retrospective study	TVUS	Excision of the adenomyotic tissue	Infertile patients with adenomyosis treated with conservative surgery and subsequent GnRH agonist treatment (3.75 mg monthly for 6 months) 100 (9/9)	/	Diffuse adenomyosis	Myometrium removed 220 g (90–240)	nr
Kishi et al. 2014 [39]	Retrospective cohort study	MRI	LPS adenomyomectomy with use of a potassium titanyl phosphate laser In case of DIE, this was removed	Group A: patients with adenomyosis desiring pregnancy < 39y 77.3 (75/97)	Group B: patients with adenomyosis desiring pregnancy > 40y 27.8 (27/97)	Adenomyoma	Adenomyoma weight 33 g (3–838) vs 92 g (2–362)	72 (54/75) vs 44.4 (12/27)
Saremi et al. 2014 [40]	Prospective study	TVUS	LPT adenomyomectomy with a thin margin (< 0.5 cm)	Symptomatic patients with adenomyosis 100 (103/103)		Localization: anterior wall, posterior wall, or both	nr	nr

Table 2 (continued)

Author, year	Study design	Diagnostic criteria	Surgery technique	Group 1	Group 2	Adenomyosis type and localization	Lesion removed weight (g) or size (cm) or volume (cm^3)	Associated endometriosis % (*n*)
Kwack et al. 2018 [19]	Retrospective analysis	TVUS	LPS or LPT adenomyomectomy with transient occlusion of the uterine artery LPT if diffuse type, or lesions size > 5 cm	Patients with focal adenomyosis treated with LPS approach and subsequent GnRH agonist treatment (3.75 mg monthly for 3 months) 49.3 (108/224)	Patients with adenomyosis (85.3% diffuse and 14.7% focal adenomyosis) treated with LPT approach and subsequent GnRH agonist treatment (3.75 mg monthly for 3 months) 51.7 (116/224)	Localization: anterior wall 29.6% vs 16.4%, posterior wall 55.6% vs 44%, fundal 14.8% vs 6.9%, whole uterus 0% vs 32.7%	Adenomyoma weight: 32.7 g vs 108.3 g Adenomyoma size: 4.34 ± 1.04 cm vs 6.48 ± 2.15 cm	11.1 (12/108) vs 31.9 (37/116)
Tskhay et al. 2018 [20]	Prospective study	TVUS, MRI, CA-125 levels	LPT triple-flap adenonomyomectomy (leaving 1 cm margin of tissue above endometrium and 1 cm margin of tissue below the serosal surface)	Infertile patients with diffuse adenomyosis 100 (18/18)	/	Diffuse adenomyosis	Myometrium removed 416.6 g ± 254.1 g	nr
Shi et al. 2021 [17]	Retrospective study	TVUS	LPS adenomyomectomy and eradication of endometriosis	Patients with adenomyosis and endometriosis, pregnancy failure 44.9 (79/176)	Patients with adenomyosis and endometriosis, successful pregnancy 55.1 (97/176)	Focal adenomyosis 46 (81/176) vs diffuse adenomyosis 54 (95/176)	nr	100 (176/176)
Won et al. 2021 [18]	Retrospective study	TVUS and MRI	LPT, LPS, or Robot assisted adenomyomectomy (leaving 1 cm margin of tissue above endometrium and 1 cm margin of tissue below the serosal surface)	Infertile patients with adenomyosis, pregnancy failure 65.1 (28/43)	Infertile patients with adenomyosis, successful pregnancy 34.9 (15/43)	Focal adenomyosis 23.2 (10/43) vs diffuse adenomyosis 76.7 (33/43)	Adenomyoma weight (pregnancy failure vs success) 123.5 g (3.0–320.0) vs 90.0 g (3.0–240.0)	28.6 (8/28) vs 53.3 (8/15)

Table 2 (continued)

Author, year	Age, mean, or median (years) ± SD	Modality of conception	Clinical pregnancy % (*n*)	Miscarriage/ clinical pregnancy % (*n*)	Live birth/clinical pregnancy % (*n*)	Mode of delivery % (*n*)	Placental malposition % (*n*)	Complications % (*n*)
Al Jama 2011 [34]	34.3 ± 4.6 vs 38.1 ± 0.9	NC	A vs B 13.6 (3/22) vs 44.4 (8/18)	A vs B 33 (1/3) vs 25 (2/8)	A vs B 33.3 (1/3) vs 75 (6/8)	Cesarean section A vs B 0 (0/1) vs 100 (6/6)	Group A: 100(1/1) retained placenta requiring manual removal	Postoperative blood transfusion (3-6 units of blood) 10 (4/40)
Osada et al. 2011 [35]	37.6 ± 6.9	IVF and NC NC 25 (4/16) IVF 75 (12/16)	61.5 (16/26)	12.5 (2/16)	87.5 (14/16)	Cesarean Sect. 100 (14/14)	nr	Small haematomas, <1 cm in the operated area, all absorbed within 2 months 5.8 (6/104)
Chang et al. 2012 [36]	38.3 ± 4.6	NC	48.2 (27/56) # Including 7 elective abortions and 1 ectopic pregnancy	14.8 (4/27)	55.5 (15/27)	nr	nr	Preterm labor 13.4 (2/15)
Dai et al. 2012 [37]	38.3	NC	2.3 (2/86)	50 (1/2) elective abortion	50 (1/2)	nr	nr	nr
Huang et al. 2012 [38]	34.2	IVF and NC	66.7 (6/9)	66.7 (4/6)	33.3 (2/6)	Cesarean Sect. 100 (2/2)	nr	nr
Kishi et al. 2014 [39]	36 (26–39) vs 42 (40–51)	IVF and NC	41.1 (42/102)	23.8 (10/42)	76.2 (32/42)	Cesarean Sect. 100 (32/32)	Placenta accreta 6.2 (2/32) treated with hysterectomy	LPT conversion 8.9 (9/102) Postoperative blood transfusion 1 (1/102) Preterm labor requinring tocolyisis 6.2 (2/32)

Table 2 (continued)

Author, year	Age, mean, or median (years) ± SD	Modality of conception	Clinical pregnancy % (*n*)	Miscarriage/ clinical pregnancy % (*n*)	Live birth/clinical pregnancy % (*n*)	Mode of delivery % (*n*)	Placental malposition % (*n*)	Complications % (*n*)
Saremi et al. 2014 [40]	37.46 ± 5.37	IVF or NC NC 33.3 (7/21) IVF 66.7 (14/21)	30 (21/70)	23.8 (5/21)[a]	76.2 (16/21)	Cesarean Sect. 100 (16/16)	nr	Asherman's syndrome 3.9 (4/103) Spontaneous uterine rupture 9.5 (2/21)
Kwack et al. 2018 [19]	42.09 ± 4.73 vs 37.49 ± 4.78	IVF or NC IVF 35.7 (5/14) NC 64.3(9/14)	6.2 (14/224) LPS 14.3 (2/14) vs LPT 85.7 (12/14)	21.4 (3/14)	78.6 (11/14)	Cesarean Sect. 100 (11/11)	nr	nr
Tskhay et al. 2018 [20]	35.66 ± 8.23 (range 24–43)	NC	16.7 (3/18)	0 (0/3)	66.7 (2/3)[b]	Cesarean Sect. 100 (2/2)[c]	nr	nr
Shi et al. 2021 [17]	33.53 ± 3.95 vs 32.52 ± 3.20	IVF or NC	67.4 (118/176)	17.8 (21/118)	82.2 (97/118)	nr	12.4 (12/97)	Preterm birth 16.5 (16/97)
Won et al. 2021 [18]	39.0 [32.0–46.0] vs 37.0 [33.0–42.0]	IVF or NC NC 6.6 (1/15) IVF 93.4 (14/15)	34.9 (15/43)[c]	20 (3/15)[c]	20 (3/15)[c]	Cesarean Sect. 100 (3/3)[c]	nr	Preterm birth 33.3 (1/3), requiring cerclage 66.7 (2/3)

Numbers are expressed as percentage (absolute value) or median ± SD or median [interquartile range] or absolute value

TVUS transvaginal ultrasound, *MRI* magnetic resonance imaging, *GnRH* gonadotropin-releasing hormone, *nr* not reported, *NC* natural conception, *LPT* laparotomy, *IVF* in vitro fertilization, *LPS* laparoscopy, *DIE* deep invasive endometriosis

[a]Includes 1 stillbirth

[b]One patient is still pregnant

[c]Some data are missing

syndrome in 3.9% (4/103) [40], and need for postoperative blood transfusion in 10% (4/40) [34] and 1% (1/102) [39], respectively. One study reported an 8.9% rate of conversion from laparoscopy to laparotomy [39]

Clinical Pregnancy Rate

Overall, the pregnancy rate was 38.1% (range 2.3–67.4%). Among women who conceived naturally [20, 34, 36, 37], the pregnancy rate was 27.9% (range 2.3–48.2%). In studies evaluating only women with diffuse adenomyosis [20, 35, 38], the pregnancy rate was 48.3% (range 16.7–66.7%), while in studies evaluating only women with focal adenomyosis [34, 36, 39], the pregnancy rate was 44.5% (range 41.1–48.2%).

Miscarriage Rate

Overall the miscarriage rate was 20.9% (range 0–66.7%). Women who conceived naturally [20, 34, 36, 37] had a miscarriage rate of 22.4% (range 0–50%). When comparing patients with diffuse adenomyosis [20, 35, 38] with those with focal adenomyosis [34, 36, 39], miscarriage rate was 6.25% (range 0–66.7%) in the former group and 21.2% (range 14.8–25%) in the latter.

Live Birth Rate

Live birth rate among all women who had undergone conservative surgery was 63.7% (range 20–87.5%). When analyzing only women who conceived naturally [20, 34, 36, 37], live birth rate was 61.8% (range 50–75%). Similarly, live birth rate was 62.5% (range 33.3–87.5%) in women with diffuse adenomyosis [20, 35, 38] and 68.9% (range 55.5–76.2%) in those with focal adenomyosis [34, 36, 39].

Mode of Delivery and Abnormal Placentation

All eight studies describing the mode of delivery reported a 100% rate of elective cesarean section among women with a previous surgical treatment of adenomyosis [18–20, 34, 35, 38–40]. Abnormal placentation rate was reported in two studies. In the first study, among 12 women with abnormal placentation (12.4%), seven had placenta previa, four had placenta accreta, and one had placenta increta [17]. In the second study, Kishi et al. reported two (6.2%) cases of placenta accreta that were managed by cesarean hysterectomy without fetal or maternal complications [39]. Two (9.5%) cases of uterine rupture in the third trimester were observed in the series by Saremi et al. [40]; one rupture occurred at 37 weeks of gestation and resulted in a stillbirth, whereas the other rupture occurred at 32 weeks and the neonate survived. In both cases, the uterus was repaired after delivery [40].

The rate of preterm delivery, in the four studies evaluating this outcome, was 6.2% [39], 16.5% [17], 13.4% [36], and 33.3% [18], respectively. Among the eight women who returned to the study center for cesarean delivery, Saremi et al. described severe adhesions in one (12.5%), moderate adhesions in two (25%), and mild adhesions in two (25%) [40].

Discussion

In agreement with previous metanalyses [3, 4], our narrative review supports the notion that, among infertile women undergoing ART, adenomyosis is associated with a poorer reproductive outcome. In this regard, the most informative studies are those comparing reproductive outcome in women affected versus not affected by adenomyosis. In the twelve studies published in the last 10 years, a better reproductive outcome was never observed in women with adenomyosis as compared to controls. Conversely, although data may not be conclusive due to the heterogenicity of study designs and population characteristics, adenomyosis was found to negatively affect all the reproductive outcomes, including implantation, pregnancy, miscarriage, and live birth rates. Interestingly, the proportion of studies showing a significant impairment ranged from a minimum of 33% demonstrating a reduced implantation rate to as much as 70% demonstrating a reduced live birth rate. Therefore, these data seem to support the notion that adenomyosis affects implantation rate less than early and late miscarriage rate and especially less than live birth rate. A tentative explanation is that women with adenomyosis suffer from a defective gestational capacity, rather than from pure subfertility. In other words, adenomyosis may not influence the quality of embryos, but it may have an adverse influence on endometrial receptivity [12••], and it may provide a dysfunctional environment for the pregnancy beyond early implantation events [15].

The hypothetical mechanisms responsible for a reduced receptivity and compliance of the pregnant uterus in women with adenomyosis include infiltration of the endometrial-myometrial junction [28], as well as an impairment of the elastic properties of the uterine wall [41]. Such detrimental anatomical conditions may be improved by the administration of GnRH agonists. Accordingly, the five studies that evaluated this issue showed that pre-treated women had an improved reproductive outcome. The proportion of studies reporting a significantly improved pregnancy rate or a reduced miscarriage rate was 20%, whereas the proportion of studies reporting a significantly improved live birth rate was 50%. Because numbers are small, it is difficult to interpret these findings from a pathogenic point of view.

However, the fact that pre-treatment with GnRH agonists resulted in a greater improvement in live birth rate as compared to pregnancy and miscarriage rates may be consistent with the hypothesis that adenomyosis negatively affects more the course of an ongoing pregnancy rather than its earlier stages. Further studies are advisable to possibly define the characteristics of women who are more likely to benefit from treatment with GnRH agonists before ART.

In one study only, pre-treatment of women with adenomyosis was accomplished by means of a LNG-IUD. Implantation, clinical pregnancy, and ongoing pregnancy rates were significantly higher in the LNG-IUD group than in the control group. Nevertheless, detrimental effects on the oocyte and/or embryo quality were suspected, but unconfirmed, in the LNG-IUD group. Further research is needed to define the role of medical pre-treatment with LNG-IUD in women with adenomyosis undergoing ART.

Other possible strategies for improving reproductive outcome of ART in infertile women with adenomyosis include long and ultra-long GnRH agonist stimulation protocols. Two studies compared pregnancy rates achieved with a long versus an ultra-long GnRH protocol: in the first study, pregnancy rate was improved for the ultra-long protocol [9••]; in the second study, no significant differences were observed [11]. Therefore, no conclusions can be drawn on which of the two protocols is associated with an improvement, if any, in reproductive outcome in women with adenomyosis. Interestingly, when analyzing infertile women with adenomyosis undergoing the long GnRH agonist protocol, Chen et al. observed a higher live birth rate in those not receiving pre-treatment with GnRH agonists compared to those receiving pre-treatment [8]. This finding, suggesting that GnRH pre-treatment may reduce the efficacy of a long GnRH stimulation protocol, needs confirmation.

Four studies evaluated the possibility of identifying women with adenomyosis who are at higher risk of an adverse reproductive outcome before beginning ART. In two studies, the authors hypothesized that the negative effect of adenomyosis on reproductive outcomes constitutes a continuum, i.e., it becomes clinically significant when a threshold of severity is reached, and it increases proportionally to the extension of disease within the myometrium [32]. In the first study, Youm et al. demonstrated that women with a myometrial thickness greater than 2.5 cm, as compared to less than 2.5 cm, presented significantly worse implantation, pregnancy, miscarriage, and live birth rates [25]. In the second study, Li et al. observed that women with a uterine volume greater than 100 cc faced significantly increased early and late abortion rates and a reduced live birth rate, whereas implantation and pregnancy rates were not affected [5]. In the remaining two studies, categorization of women based on adenomyosis location (extrinsic or intrinsic or diffuse) and a serum CA 125 value greater or lower than 35 were not predictive of an impaired outcome of ART [7, 33]. Surprisingly, among the three studies comparing women with diffuse adenomyosis and women with focal adenomyosis, no difference in reproductive outcomes was observed between the two groups [11, 29, 31].

Further research should be carried out to establish standardized, easy to implement, widely agreed on, and reliable criteria for the categorization of adenomyosis and the prediction of affected women's reproductive potential. This seems important to adequately counsel women with adenomyosis and to guide them through a shared decision-making process, in the choice between natural conception, conservative surgery, and assisted reproduction, or a combination of these options.

The analysis including a total of 961 women demonstrates the possibility to achieve and carry out a successful pregnancy after surgical removal of adenomyosis. The overall mean pregnancy rate in these patients is substantially similar to that observed in women not operated on (38.1% vs 39.4%). Therefore, surgical treatment does not seem to impact negatively on pregnancy rate in women with adenomyosis. In this regard, it is important to separately evaluate the reproductive outcome of women who underwent conservative surgery for focal adenomyosis from that of women who underwent surgery for diffuse adenomyosis. In fact, surgical removal of focal adenomyosis is easier and usually allows to restore normal uterine anatomy; on the other hand, surgical removal of diffuse adenomyosis may often be challenging and not radical. Nevertheless, according to available evidence, pregnancy rates after surgical removal of focal (44%) [34, 36, 39] versus diffuse (48%) [20, 35, 38] adenomyosis do not seem to differ and also appear comparable to the pregnancy rate observed in non-operated women. Furthermore, birth rates as high as 69% and 62% were observed among women who had undergone surgery for focal and diffuse adenomyosis, respectively. This data suggests that the surgical removal of adenomyosis may be effective in making the uterus a more functional environment for both implantation and maintenance of pregnancy. However, women operated on appear to face a not negligible risk of potentially severe complications of pregnancy such as placenta previa, placenta accreta, uterine rupture, and significant adhesions. For this reason, in our opinion, it is important that the management of ongoing pregnancies and especially deliveries of women who have undergone conservative surgical treatment of adenomyosis are carried out by experienced surgeons in referral centers with a neonatal intensive care unit and a blood bank.

In conclusion, available evidence shows that adenomyosis negatively affects reproductive outcome. Pre-treatment with GnRH agonists is advantageous in improving reproductive outcome in infertile women with adenomyosis undergoing ART, but the actual magnitude of such improvement needs to be better defined. Conservative surgical treatment of both focal and diffuse adenomyosis has been associated

with similar pregnancy rates and improved live birth rates when compared to women who have not undergone surgery, although data is based on a limited number of studies.

Author Contribution NB and PV were responsible for conception and design of the study and for critical revision of the article for intellectual content. Acquisition of data was performed by AD, FF, and DD. Analysis and interpretation of data were accomplished by GEC. All the authors approved the final version of the manuscript.

Declarations

Competing Interests The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies on animal subjects.

References

Papers of particular interest, published recently, have been highlighted as:
•• Of major importance

1. Campo S, Campo V, Benagiano G. Adenomyosis and infertility. Reprod Biomed Online. 2012;24:35–46. https://doi.org/10.1016/j.rbmo.2011.10.003.
2. Harada T, Khine YM, Kaponis A, Nikellis T, Decavalas G, Taniguchi F. The impact of adenomyosis on women's fertility. Obstet Gynecol Surv. 2016;71:557–68. https://doi.org/10.1097/OGX.0000000000000346.
3. 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. https://doi.org/10.1093/humrep/deu041.
4. Younes G, Tulandi T. Effects of adenomyosis on in vitro fertilization treatment outcomes: a meta-analysis. Fertil Steril. 2017;108:483-490.e3. https://doi.org/10.1016/j.fertnstert.2017.06.025.
5. Li X, Pan N, Zhang W, Wang Y, Ge Y, Wei H, Lin Y, Ma C. Association between uterine volume and pregnancy outcomes in adenomyosis patients undergoing frozen-thawed embryo transfer. Reprod Biomed Online. 2021;42:384–9. https://doi.org/10.1016/j.rbmo.2020.10.002.
6. Li M, Xu L, Zhao H, Du Y, Yan L. Effects of artificial cycles with and without gonadotropin-releasing hormone agonist pretreatment on frozen embryo transfer outcomes in patients with adenomyosis. Sci Rep. 2021;11:19326. https://doi.org/10.1038/s41598-021-98918-5.
7. Iwasawa T, Takahashi T, Maeda E, Ishiyama K, Takahashi S, Suganuma R, Matsuo K, Tachibana M, Fukuhara R, Shirasawa H, Sato W, Kumazawa Y, Terada Y. Effects of localisation of uterine adenomyosis on outcome of in vitro fertilisation/intracytoplasmic sperm injection fresh and frozen-thawed embryo transfer cycles: a multicentre retrospective cohort study. Reprod Biol Endocrinol. 2021;19:84. https://doi.org/10.1186/s12958-021-00764-7.
8. Chen M, Luo L, Wang Q, Gao J, Chen Y, Zhang Y, Zhou C. Impact of gonadotropin-releasing hormone agonist pre-treatment on the cumulative live birth rate in infertile women with adenomyosis treated with IVF/ICSI: a retrospective cohort study. Front Endocrinol. 2020;11:318. https://doi.org/10.3389/fendo.2020.00318.
9. •• Hou X, Xing J, Shan H, Mei J, Sun Y, Yan G, et al. The effect of adenomyosis on IVF after long or ultra-long GnRH agonist treatment. Reprod Biomed Online. 2020;41:845–853. https://doi.org/10.1016/j.rbmo.2020.07.027. **Findings from this study suggest that, among women with adenomyosis undergoing ART, pregnancy outcome is improved by an ultra-long rather than a long GnRH agonist protocol.**
10. Neal S, Morin S, Werner M, Gueye NA, Pirtea P, Patounakis G, et al. Three-dimensional ultrasound diagnosis of adenomyosis is not associated with adverse pregnancy outcome following single thawed euploid blastocyst transfer: prospective cohort study. Ultrasound Obstet Gynecol. 2020;56:611–7. https://doi.org/10.1002/uog.22065.
11. Lan J, Wu Y, Wu Z, Wu Y, Yang R, Liu Y, Lin H, Jiao X, Zhang Q. Ultra-long GnRH agonist protocol during IVF/ICSI improves pregnancy outcomes in women with adenomyosis: a retrospective cohort study. Front Endocrinol. 2021;12: 609771. https://doi.org/10.3389/fendo.2021.609771.
12. •• Zhang J, Hu L, Bu Z, Sun Y. Impact of uterine adenomyosis on pregnancy outcomes in women undergoing in vitro fertilization treated with a long-term pituitary downregulation protocol. Front Endocrinol. 2021;12:655–803. https://doi.org/10.3389/fendo.2021.655803. **Findings from this study suggest that, among women undergoing IVF and pre-treated with GnRH agonists, adenomyosis is more detrimental than endometriosis on reproductive outcome.**
13. Zhang XP, Zhang YF, Shi R, Zhang YJ, Zhang XL, Hu XM, Hu XY, Hu YJ. Pregnancy outcomes of infertile women with ultrasound-diagnosed adenomyosis for in vitro fertilization and frozen-thawed embryo transfer. Arch Gynecol Obstet. 2021;304:1089–96. https://doi.org/10.1007/s00404-021-06011-z.
14. Liang Z, Yin M, Ma M, Wang Y, Kuang Y. Effect of pretreatment with a levonorgestrel-releasing intrauterine system on IVF and vitrified-warmed embryo transfer outcomes in women with adenomyosis. Reprod Biomed Online. 2019;39:111–8. https://doi.org/10.1016/j.rbmo.2019.03.101.
15. Stanekova V, Woodman RJ, Tremellen K. The rate of euploid miscarriage is increased in the setting of adenomyosis. Hum Reprod Open. 2018:hoy011. https://doi.org/10.1093/hropen/hoy011
16. Sharma S, Bathwal S, Agarwal N, Chattopadhyay R, Saha I, Chakravarty B. Does presence of adenomyosis affect reproductive outcome in IVF cycles? A retrospective analysis of 973 patients. Reprod Biomed Online. 2019;38:13–21. https://doi.org/10.1016/j.rbmo.2018.09.014.
17. Shi J, Dai Y, Zhang J, Li X, Jia S, Leng J. Pregnancy outcomes in women with infertility and coexisting endometriosis and adenomyosis after laparoscopic surgery: a long-term retrospective follow-up study. BMC Pregnancy Childbirth. 2021;21:383. https://doi.org/10.1186/s12884-021-03851-0.
18. Won S, Hwang JY, Lee N, Kim M, Kim MK, Kim ML, Yun BS, Seong SJ, Jung YW. Anti-Müllerian hormone level may predict successful pregnancy after adenomyomectomy in patients with infertility due to adenomyosis. Medicine (Baltimore). 2021;28(100): e26075. https://doi.org/10.1097/MD.0000000000026075.
19. Kwack JY, Im KS, Kwon YS. Conservative surgery of uterine adenomyosis via laparoscopic versus laparotomic approach in a single institution. J Obstet Gynaecol Res. 2018;44:1268–73. https://doi.org/10.1111/jog.13658.
20. Tskhay V, Schindler AE, Mikailly G. Operation, hormone therapy and recovery of the patients with severe forms of adenomyosis. Gynecol Endocrinol. 2018;34:647–50. https://doi.org/10.1080/09513590.2017.1397116.
21. Van den Bosch T, Dueholm M, Leone FP, Valentin L, Rasmussen CK, Votino A, et al. Terms, definitions and measurements to describe sonographic features of myometrium and uterine masses:

a consensus opinion from the Morphological Uterus Sonographic Assessment (MUSA) group. Ultrasound Obstet Gynecol. 2015;46:284–98. https://doi.org/10.1002/uog.14806.
22. Bazot M, Daraï E. Role of transvaginal sonography and magnetic resonance imaging in the diagnosis of uterine adenomyosis. Fertil Steril. 2018;109:389–97. https://doi.org/10.1016/j.fertnstert.2018.01.024.
23. 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. https://doi.org/10.1016/j.ejogrb.2011.04.030.
24. Martínez-Conejero JA, Morgan M, Montesinos M, Fortuño S, Meseguer M, Simón C, Horcajadas JA, Pellicer A. Adenomyosis does not affect implantation, but is associated with miscarriage in patients undergoing oocyte donation. Fertil Steril. 2011;96:943–50. https://doi.org/10.1016/j.fertnstert.2011.07.1088.
25. 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. https://doi.org/10.1007/s10815-011-9640-7.
26. 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. https://doi.org/10.1016/j.rbmo.2012.05.003.
27. 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. https://doi.org/10.1093/humrep/des305.
28. 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. https://doi.org/10.3109/09513590.2013.824960.
29. Benaglia L, Cardellicchio L, Leonardi M, Faulisi S, Vercellini P, Paffoni A, Somigliana E, Fedele L. Asymptomatic adenomyosis and embryo implantation in IVF cycles. Reprod Biomed Online. 2014;29:606–11. https://doi.org/10.1016/j.rbmo.2014.07.021.
30. 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. https://doi.org/10.1159/000355101.
31. 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. https://doi.org/10.5653/cerm.2016.43.3.169.
32. Mavrelos D, Holland TK, O'Donovan O, Khalil M, Ploumpidis G, Jurkovic D, Khalaf Y. The impact of adenomyosis on the outcome of IVF-embryo transfer. Reprod Biomed Online. 2017;35:549–54. https://doi.org/10.1016/j.rbmo.2017.06.026.
33. Huang L, Li Y, Chen M, Wang Z, Zhou C. Serum levels of cancer antigen 125 before hormone replacement therapy are not associated with clinical outcome of frozen embryo transfer in women with adenomyosis. J Int Med Res. 2021;49:3000605211005878. https://doi.org/10.1177/03000605211005878.
34. Al Jama FE. Management of adenomyosis in subfertile women and pregnancy outcome. Oman Med J. 2011;26:178–81. https://doi.org/10.5001/omj.2011.43.
35. Osada H, Silber S, Kakinuma T, Nagaishi M, Kato K, Kato O. Surgical procedure to conserve the uterus for future pregnancy in patients suffering from massive adenomyosis. Reprod Biomed Online. 2011;22:94–9. https://doi.org/10.1016/j.rbmo.2010.09.014.
36. Chang WH, Wang KC, Lee NR, Huang N, Su WH, Chao HT, Yen MS, Fuh JL, Wang PH. Reproductive performance of severely symptomatic women with uterine adenomyoma who wanted preservation of the uterus and underwent combined surgical-medical treatment. Taiwan J Obstet Gynecol. 2013;52:39–45. https://doi.org/10.1016/j.tjog.2013.01.007.
37. Dai Z, Feng X, Gao L, Huang M. Local excision of uterine adenomyomas: a report of 86 cases with follow-up analyses. Eur J Obstet Gynecol Reprod Biol. 2012;161:84–7. https://doi.org/10.1016/j.ejogrb.2011.11.028.
38. Huang BS, Seow KM, Tsui KH, Huang CY, Lu YF, Wang PH. Fertility outcome of infertile women with adenomyosis treated with the combination of a conservative microsurgical technique and GnRH agonist: long-term follow-up in a series of nine patients. Taiwan J Obstet Gynecol. 2012;51:212–6. https://doi.org/10.1016/j.tjog.2012.04.008.
39. Kishi Y, Yabuta M, Taniguchi F. Who will benefit from uterus-sparing surgery in adenomyosis-associated subfertility? Fertil Steril. 2014;102:802-807.e1. https://doi.org/10.1016/j.fertnstert.2014.05.028.
40. Saremi A, Bahrami H, Salehian P, Hakak N, Pooladi A. Treatment of adenomyomectomy in women with severe uterine adenomyosis using a novel technique. Reprod Biomed Online. 2014;28:753–60. https://doi.org/10.1016/j.rbmo.2014.02.008.
41. Xie M, Yu H, Zhang X, Wang W, Ren Y. Elasticity of adenomyosis is increased after GnRHa therapy and is associated with spontaneous pregnancy in infertile patents. J Gynecol Obstet Hum Reprod. 2019;48:849–53. https://doi.org/10.1016/j.jogoh.2019.05.003.