Title
Adenomyosis and fertility: does adenomyosis impact fertility and does treatment improve outcomes.

Journal
Current opinion in obstetrics & gynecology, 34(4)

ISSN
1040-872X

Authors
French, Hannah M
Zhang, Wenjia
Movilla, Peter R
et al.

Publication Date
2022-08-01

DOI
10.1097/gco.0000000000000789

Adenomyosis and fertility: does adenomyosis impact fertility and does treatment improve outcomes

Hannah M. French, Wenjia Zhang, Peter R. Movilla, Keith B. Isaacson, and Stephanie N. Morris

Purpose of review
Adenomyosis has recently been associated with infertility. Relief of bleeding and pain has been demonstrated with medical and surgical therapy. Less is known about reproductive outcomes after treatment.

Recent findings
Imaging findings during infertility evaluation can be suggestive of adenomyosis without pathologic evaluation. Among women with infertility undergoing assisted reproductive technologies (ART), adenomyosis is associated with lower live birth rates and clinical pregnancy rates. Treatment with gonadotropin releasing hormone (GnRH) modulators prior to frozen embryo transfer may increase the live birth rate and clinical pregnancy rate among women with adenomyosis. Pregnancy has been documented following image-guided adenomyosis ablation; however, the reproductive impact is not well established. Pregnancy following excisional procedures appears to be well tolerated, although may carry a higher risk of uterine rupture compared with pregnancy following myomectomy. It is not clear if ablative therapy or resection increases pregnancy rates.

Summary
Adenomyosis is associated with lower embryo implantation rates and ongoing pregnancy rates. Adenomyotic changes in the uterus can be seen by ultrasound and MRI. GnRH modulators may be useful for women with adenomyosis undergoing ART. Additional prospective data is warranted to determine the optimal medical or surgical therapy for women with adenomyosis desiring conception.
Video abstract Supplementary digital content, http://links.lww.com/COOG/A78.

Keywords
adenomyosis, in-vitro fertilization, infertility, ultrasound

INTRODUCTION

Adenomyosis describes the disorder wherein endometrial glands and stroma are abnormally located in the uterine myometrium. Adenomyosis leads to changes in the endometrium and abnormal uterine contractility, which can cause dysmenorrhea, abnormal uterine bleeding, and infertility. Changes in the uterine morphology thought to be because of the presence of adenomyosis can be seen by transvaginal ultrasound (TVUS) and MRI in women undergoing infertility evaluation. Treatment of adenomyosis in patients with infertility may improve reproductive outcomes. The primary objective of this review is to summarize the impact of adenomyosis on fertility and the impact of treatment on reproductive outcomes.

BACKGROUND

In adenomyosis, ectopic endometrial glands and stroma are associated with changes in the surrounding myometrium [1]. Altered tissue structure and function at the endometrial myometrial junction may impact fertility and reproductive outcomes. Among women with infertility, adenomyosis has been associated with a lower clinical pregnancy rate, higher miscarriage rate, and lower live birth rate [2▪–4▪]. Additionally, adenomyosis may be associated with obstetric complications, such as abnormal placentation [5▪]. Historically, adenomyosis was a histologic diagnosis made at the time of hysterectomy. Now, changes associated

Minimally Invasive Gynecologic Surgery, Women's Health Center, Newton-Wellesley Hospital, Newton, Massachusetts, USA

Correspondence to Hannah M. French, MD, Fellow, Minimally Invasive Gynecologic Surgery, Women's Health Center, Newton-Wellesley Hospital, 2014 Washington Street, Newton, MA 02462, USA.
Tel: +1 617 243 498; fax: +1 617 243 5029;
e-mail: Hfrench1@partners.org

Curr Opin Obstet Gynecol 2022, 34:227–236
DOI:10.1097/GCO.0000000000000789

KEY POINTS

- Adenomyosis-associated uterine changes can be visualized using transvaginal ultrasound and MRI, though there is no consensus regarding the specific features and number of features required for diagnosis.
- Adenomyosis is associated with decreased live birth rates among women undergoing IVF.
- GnRH agonist treatment may improve reproductive outcomes among women with adenomyosis undergoing IVF; however, the data is mixed for duration of therapy and fresh versus frozen cycles.
- Although pregnancy has been documented following image-guided ablation and excision of adenomyosis, risks of pregnancy after treatment and impact on infertility are not well established.
- Adenomyosis and endometriosis often co-occur, and the presence of both entities is associated with worse infertility.

with adenomyosis can be seen using imaging in women who may desire future fertility [6▪▪].

INCIDENCE AND PREVALENCE

Estimates regarding the incidence and prevalence of adenomyosis vary widely. A US population-based study of women ages 16–60 years found a 1% incidence of adenomyosis [7]. A recent systematic review estimated prevalence from 15 to 67%. This wide range is attributable to multiple factors, such as different diagnostic criteria and inclusion of symptomatic versus asymptomatic patients [8▪].

Although many women are asymptomatic, associated symptoms include dysmenorrhea, abnormal uterine bleeding, and infertility. In a cohort of women 18–42 years undergoing benign gynecologic surgery, the prevalence of infertility was estimated at 30% (75/248) among women with adenomyosis [9▪]. The prevalence of adenomyosis among patients with infertility increases with age [10].

IMAGING FINDINGS

The gold standard for diagnosis of adenomyosis is histology from hysterectomy specimens. Additional diagnostic tools include directed tissue sampling through hysteroscopic or laparoscopic biopsy; however, biopsy is not routinely used because of poor sensitivity [11]. More recently, features seen on TVUS and MRI have been used for diagnosis of adenomyosis without histologic confirmation, which is of particular importance to patients with infertility who are seeking uterine-conserving diagnosis and treatment. There is no consensus regarding the specific features or number of features for diagnosis of adenomyosis using imaging. The lack of consensus makes interpretation of research publications challenging, as studies utilize different imaging criteria to define adenomyosis. Here we summarize recent advances in imaging that the clinician may utilize for diagnosis and the estimated sensitivity and specificity of different techniques.

Ultrasound

In 2015, the Morphological Uterus Sonographic Assessment (MUSA) group introduced consensus terminology to describe the myometrium using ultrasound (US), such as asymmetrical myometrial thickening, myometrial cysts, hyperechoic islands, fan-shaped shadowing, echogenic subendometrial lines and buds, translesional vascularity, and an irregular junctional zone [12]. The junctional zone describes the appearance of the interface between the endometrium and the myometrium on both TVUS and MRI.

The diagnostic accuracy of adenomyosis on TVUS compared with histologic confirmation has sensitivity and specificity ranging from 11–85% to 25–98%, respectively [13▪,14,15]. Addition of US technologies, such as 3D TVUS, elastography, and Doppler studies may increase TVUS accuracy for detecting adenomyosis. 3D TVUS can help evaluate the junctional zone and increase diagnostic accuracy [15,16▪,17▪]. Elastography has been proposed to help differentiate between fibroids and adenomyosis, with mixed results [16▪,18▪]. The results of recent studies investigating accuracy of different TVUS criteria are summarized in Table 1. Heterogeneous myometrium and uterine wall asymmetry appear to have the highest sensitivity and specificity.

MRI

US and MRI have comparable accuracy for diagnosing adenomyosis [16▪,19,20▪]. Features of adenomyosis on MRI include an enlarged asymmetric globular uterus, the presence of cysts or foci on T1 or T2 weighted images, and increased junctional zone thickness, typically greater than 12 mm [21▪]. A prospective study looking at MRI compared with hysterectomy samples found that junctional zone thickness was not correlated to a diagnosis of adenomyosis, and instead the presence of an irregular junctional zone had the best association with adenomyosis (sensitivity 74%, specificity 83%) [22]. MRI also has been used to specify the location and extent of adenomyosis [23]. Similar to US

Table 1. Transvaginal ultrasound accuracy in diagnosing adenomyosis

	Overall accuracy		Ultrasound feature accuracy		
First author, year	**Sensitivity (%)**	**Specificity (%)**	**US feature**	**Sensitivity (%)**	**Specificity (%)**
Sam, 2020	37	92	Bulky uterus	77	59
			Heterogeneous myometrium	75	57
			Myometrial cysts	33	89
			Streaky uterus	34	93
			Subendometrial echogenic striations	32	93
			Ill-definition of endometrial–myometrial interface	44	81
Liu, 2021	81	87	Asymmetrical thickening	44	79
			Myometrial cysts	54	93
			Hyperechoic islands	NA	NA
			Fan-shaped shadowing	NA	NA
			Echogenic subendometrial lines and buds	40	92
			Translesional vascularity	NA	NA
			JZ abnormalities	64	73
Da silva, 2021	31	91	Myometrial cysts	18	98
			Asymmetry of uterine wall	7	99
			Heterogeneous myometrium	82	19
			Hypoechoic linear striation	2	97
			Globular uterus	11	72
Zannoni, 2020	77	96	Globular shape	77	46
			Asymmetry	80	70
			Heterogeneous myometrium	100	7
			Poorly defined interface	85	56
			Fan-shaped striations	54	96
			Myometrial cysts	30	92
			Question mark sign	41	96
			Tenderness	69	65
			JZ at least −8 mm	40	99
			JZ interruption	70	88
			ΔJZ	60	87
			Doppler	55	88
Chapron, 2020	65–84	64–100	Asymmetric myometrial wall	57	72
			Myometrial cysts	72	63
			Hypoechoic linear striation	71	80
			Heterogeneous myometrium	86	61
			Poor definition JZ	59	80
			Question mark sign	75	92
			3D TVUS		
			Asymmetric myometrial wall	59	53
			Myometrial cysts	58	54
			Hypoechoic linear striation	53	61
			Heterogeneous myometrium	83	41
			Poor definition JZ	88	56

JZ, junctional zone; TVUS, transvaginal ultrasound.
[a]NA, not applicable.

criteria, there is no consensus regarding specific MRI features required for diagnosis, although junctional zone thickness and irregularity appear most accurate for diagnosis.

The reported accuracy of imaging findings for the diagnosis of adenomyosis varies greatly and there is no universally agreed upon diagnostic criteria. Studies looking at the impact of adenomyosis on infertility define adenomyosis based on any or a minimum number of imaging findings on TVUS and MRI.

PATHOGENESIS OF ADENOMYOSIS AND INFERTILITY: PROPOSED MECHANISMS

Although the cause of adenomyosis is debated, the presence of adenomyosis is associated with predictable molecular changes in the endometrium and surrounding myometrium leading to abnormal function [24–26]. Dysmenorrhea is thought to be a result of myometrial hypercontractility, while abnormal uterine bleeding is thought to be related to neoangiogenesis, abnormal uterine contractility and high microvessel density [25]. Adenomyosis may contribute to infertility and poor embryo implantation. Proposed mechanisms include abnormal contractility, alterations in the uterine environment, increased inflammation, and abnormal endometrial receptivity [25,26].

The myometrium is constituted of the inner and outer myometrium. A derivative of the Mullerian system, the inner myometrium is hormonally responsive to changes in the menstrual cycle. The inner myometrium exhibits cervical to fundal contractions during the follicular phase to facilitate sperm transport, and fundal to cervical contractions during the luteal phase to facilitate menstruation. Adenomyotic lesions induce a response leading to myometrial hypertrophy and abnormal hormone signaling, which may be associated with abnormal contractility [24]. Abnormal contractions of the inner myometrium may contribute to altered sperm transport and decreased implantation [26,27▪,28▪].

Abnormal hormone signaling pathways involving estrogen and progesterone receptors in the inner myometrium, dysregulation of immune factors, and increased inflammatory oxidative stress may lead to reduced uterine receptivity for implantation [25,26]. Epigenetic changes in the endometrium seen in adenomyosis, such as downregulation of Hox-A10, may lead to disordered decidualization and thereby reduce endometrial receptivity [26]. Animal models suggest that targeting the pathway leading to fibrosis may improve endometrial receptivity [29▪]. This complex disease of inflammation, fibrosis, and altered hormonal signaling provides multiple areas to target for future study and treatment.

TREATMENT OF ADENOMYOSIS FOR PATIENTS WITH INFERTILITY

Therapies for adenomyosis target different features of the disease process. Medical therapies include a diverse array of options ranging from antiplatelet agents to hormonal agents. Techniques for destruction of adenomyotic lesions include uterine artery embolization (UAE), thermal ablation, and resection through hysteroscopy, laparoscopy, or laparotomy. Although medical and surgical treatments have been demonstrated to relieve bleeding and pain, less is known about reproductive outcomes.

Medical treatment

In women undergoing in-vitro fertilization (IVF), adenomyosis appears to be associated with lower live birth rate, although not all studies have demonstrated this association [2▪–4▪,30▪]. The majority of recent data regarding reproductive outcomes after medical treatment of adenomyosis comes from pretreatment with GnRH agonists in women undergoing assisted reproductive technology (ART) and IVF, summarized in Table 2.

GnRH modulators may improve reproductive outcomes among women with adenomyosis undergoing IVF. In a large retrospective cohort, pretreatment with an ultra-long GnRH-agonist (2–4 months prior to embryo transfer) compared with a long GnRH-agonist (single dose given in the preceding cycle luteal phase prior to ovarian stimulation) improved the live birth rate, 43 vs. 26%, $P = 0.019$, and clinical pregnancy rate, 55 vs. 38%, $P = 0.025$ [31▪]. In a similar retrospective cohort, an ultra-long GnRH agonist protocol compared with a long agonist protocol was also associated with increased live birth rate and clinical pregnancy rate with fresh transfer [32▪]. The impact of GnRH-agonist pretreatment on live birth rate and clinical pregnancy rate may be different for fresh and frozen cycles [33▪].

One recent retrospective cohort demonstrated no difference in outcome using GnRH-agonist pretreatment in frozen embryo transfer; however, this cohort had a wide range of pretreatment ranging from one dose of leuprolide acetate in the preceding cycle up to several monthly injections of a GnRH agonist prior to transfer [34▪]. Another retrospective trial found lower live birth rate and clinical pregnancy rate in patients who underwent GnRH-agonist pretreatment (up to three monthly doses) versus no pretreatment in a fresh transfer cycle [35].

Table 2. Reproductive outcomes among women with adenomyosis undergoing in-vitro fertilization

First author, year	Design	Study population	Number of subjects	Intervention	Live birth rate (%)	Clinical pregnancy rate (%)	Diagnosis of adenomyosis	Notes
Lan, 2021	Retrospective cohort	Adenomyosis undergoing IVF/ICSI cycle, fresh transfer	328 –212 with ultra-long GnRH-agonist -116 with long GnRH-agonist	Ultra-long GnRH-agonist protocol (long acting diphereline 3.75 mg subcutaneously every month for 2–4 months) vs. long GnRH-agonist protocol (single dose diphereline In diffuse vs. focal adenomyosis	44 vs. 26, $P=0.019$	56 vs. 38, $P=0.025$	US findings of: -enlarged globular uterine configuration -asymmetrical thickening of uterine walls -poor definition of junctional zone -heterogeneous myometrial texture -sub-endometrial myometrial striations and cysts	Equivocal US diagnosis confirmed with MRI Split groups into focal and diffuse adenomyosis Increased LBR and CP in women with diffuse adenomyosis using ultra-long GnRH-agonist; no difference was seen in focal adenomyosis group
Hou, 2020	Retrospective cohort	Adenomyosis undergoing first cycle of IVF/ICSI, fresh transfer, control with tubal infertility	3960 -489 with adenomyosis -3471 controls	Adenomyosis ultra-long GnRH-agonist protocol (long-acting triptorelin acetate every 28 days for ≥3 months before ovarian stimulation) vs. adenomyosis long GnRH-agonist protocol (daily short-acting tritorelin during the mid-luteal phase of the previous cycle)	52 vs. 38, $P<0.001$	64 vs. 51, $P<0.001$	Clinical symptoms (bleeding, pain); enlarged uterus; and ≥2 2D US findings: -nondistinct endometrial-myometrial junction -asymmetric anterior and posterior myometrium -subendometrial myometrial striations -myometrial cysts and fibrosis -heterogeneous myometrial echotexture	Two 2D US performed to confirm diagnosis Compared with control group (tubal infertility undergoing long GnRH agonist protocol), adenomyosis with long protocol showed lower clinical pregnancy rate Compared with adenomyosis with long protocol, ultra-long protocol showed increased LBR and CP
Neal, 2020	Prospective cohort	Adenomyosis undergoing IVF, frozen euploid blastocyst transfer	648 -99 with adenomyosis -549 without adenomyosis	Transfer single thawed euploid blastocyst in women with vs. without adenomyosis	70 vs. 67, $P=0.57$	80 vs. 75, $P=0.29$	3D US: -global uterine enlargement -myometrial wall asymmetry -heterogeneous echogenicity -irregular junctional zone -myometrial cysts -fan-shaped shadowing and ill-defined myometrial lesions	3D US performed day prior to embryo transfer, with prevalence of adenomyosis 15.3% (99/648) Most women asymptomatic Diagnosis of adenomyosis required only one of seven features seen on US Three IVF protocols (oral estradiol 2 mg twice daily; natural cycle; GnRH agonist downregulation with leuprolide acetate 0.5 mg twice daily in luteal phase of prior cycle followed by oral estradiol 2 mg twice daily)
Chen, 2020	Retrospective cohort	Adenomyosis undergoing IVF/ICSI with fresh embryo transfer	374 (with adenomyosis)	Fresh embryo transfer using long GnRH-agonist protocol in patients with GnRH-agonist pretreatment (up to three monthly doses of triptorelin acetate 3.75 mg) vs. no pretreatment	21 vs. 38, $P=0.028$	28 vs. 41, $P=0.019$	US criteria: -heterogeneous myometrial area -globular asymmetric uterus -irregular cystic spaces -myometrial linear striations -poorly defined endometrial myometrial junction -asymmetry of anterior and posterior myometrium -abnormal echogenicity	Measured myometrial thickness during pretreatment and if thickened continued with up to 3 months of GnRH agonist pretreatment

Table 2 (*Continued*)

First author, year	Design	Study population	Number of subjects	Intervention	Live birth rate (%)	Clinical pregnancy rate (%)	Diagnosis of adenomyosis	Notes
Li, 2021	Retrospective	Adenomyosis undergoing IVF	341 (with adenomyosis)	Adenomyosis with GnRH-a pretreatment (leuprolide acetate 3.75 mg) vs. hormone replacement to prepare endometrium	24 vs. 24, $P=0.74$	41 vs. 43, $P=0.72$	2D US criteria -subjective enlargement of uterine corpus -asymmetric thickening of anterior and posterior myometrium -heterogeneous myometrium -hypoechoic striations -poorly defined endometrial–myometrial junction	Additional pretreatment with GnRH agonist (leuprolide acetate or triptorelin) in patients with larger uteri, with multiple monthly injections prior to receiving leuprolide in the cycle before transfer Wide variety of ovulation stimulation protocols
Wu, 2021	Retrospective	Adenomyosis undergoing IVF/ICSI	537 (with adenomyosis)	Adenomyosis with pretreatment with GnRH-agonist (gosrelin 3.75 mg monthly) and frozen embryo transfer vs. ultra-long GnRH agonist (dipherelin 3.75 mg monthly for at least 3 months before ovarian stimulation) and fresh vs. long GnRH agonist (triptorelin depot or daily) and fresh	51 vs. 41 vs. 33.9, $P=0.007$	60 vs. 54 vs. 44, $P=0.023$	Clinical signs and US criteria: -asymmetric uterine wall thickness -myometrial cysts -myometrial hyperechogenic islands -fan shaped shadowing -subendometrial lines and buds -translesional vascularity -irregular junctional zone -junctional zone interruption at multiple sites	At least two US criteria for diagnosis MRI performed for diagnosis if equivocal US In pretreatment and ultra-long group, GnRH agonist was administered for at least 3 months and up to 4 months if anteroposterior diameter >70mm Most subjects in pretreatment and ultralong groups received 3 months GnRH agonist before transfer

GnRH, gonadotropin-releasing hormone; ICSI, intracytoplasmic sperm injection; IVF, in-vitro fertilization; JZ, junctional zone; TVUS, transvaginal ultrasound.

Although GnRH-agonist pretreatment appears to improve live birth rate among women with adenomyosis pursuing IVF, future prospective data would better inform the choice of GnRH modulator, duration of treatment, and use prior to fresh or frozen cycle.

Regression of adenomyosis evidenced by a decrease in uterine size may represent a treatment goal prior to pregnancy. Larger uterine volume because of adenomyosis has been associated with decreased live birth rate in the setting of IVF [36▪]. However, prospective study is required to understand if a decrease in uterine size improves fertility or pregnancy outcomes.

Uterine artery embolization

Well studied as a treatment for uterine fibroids, uterine artery embolization (UAE) has recently been shown to reduce symptoms associated with adenomyosis, such as bleeding and dysmenorrhea. Although successful pregnancy has been demonstrated in retrospective cohorts following UAE for adenomyosis, the incidence of obstetric complications, such as placental abnormalities and preterm labor may be increased [37▪,38▪] Additional prospective data is needed to determine if pregnancy after UAE for adenomyosis is well tolerated and improves pregnancy rates.

Image-guided thermal ablation

The increasing success of image guided thermal ablation for bleeding and dysmenorrhea associated with adenomyosis has raised questions about pregnancy outcomes after treatment [39]. Techniques for image-guided thermal ablation include high-intensity focused ultrasound (HIFU), MRI-guided focused ultrasound, ultrasound-guided radiofrequency ablation, and percutaneous microwave ablation. In HIFU and MRI-guided focused ultrasound, the ultrasound probe induces a temperature rise at the target tissue causing coagulative necrosis. In radiofrequency ablation and percutaneous microwave ablation, an instrument is inserted into a lesion to raise the temperature and cause tissue destruction.

Reproductive outcomes for each technique are limited. A recent systematic review and meta-analysis documented pregnancy rates following thermal ablation of 17% (HIFU), 5% (microwave ablation), and 36% (radiofrequency ablation); however, the primary outcomes of most studies included impact on bleeding and pain rather than the impact on pregnancy outcomes [40▪]. A retrospective cohort of 81 patients who underwent radiofrequency ablation for adenomyosis and desired future fertility noted that 36% of the cohort achieved pregnancy with a live birth rate among women who conceived of 67% [41]. Another systematic review and meta-analysis of HIFU noted that anti-Mullerian hormone was unchanged after HIFU; however, only one series reported pregnancy outcomes including six total pregnancies [42]. In a retrospective cohort of 93 patients with adenomyosis who underwent HIFU vs. laparoscopic excision, the rate of pregnancy was 52. vs. 30%, $P = 0.034$. Of note, patients were treated with a GnRH-agonist following HIFU or laparoscopy, which may have influenced reproductive outcomes [43]. In summary, pregnancy may be safe after image-guided thermal ablation, though it is not clear if treatment improves fertility or pregnancy outcomes.

Excisional techniques

Surgical resection of focal and diffuse adenomyosis reduces vaginal bleeding, pain, and uterine volume [44]. Sparse data exists for reproductive outcomes after excisional therapy and is largely from retrospective cohorts.

Hysteroscopy could be considered for resection of cystic or solid lesions close to the endometrial cavity, though this has not been studied prospectively in terms of reproductive outcomes. Laparoscopic or open approaches can be used to resect focal lesions via adenomyomectomy or diffuse lesions using a wedge excision, classical incision, or flap reconstruction. Obstetric risks following excision of adenomyosis may be similar to myomectomy in which the uterine muscle is incised and repaired. Possible sequelae include uterine rupture, abnormal placentation, or intrauterine adhesive disease. Reported rates of uterine rupture following adenomyosis excision vary widely, from 0 to 13% depending on the patient cohort referenced, which is generally higher than following myomectomy [45].

A recent systematic review suggested that pregnancy is likely safe after excisional procedures with low rates of uterine rupture (1/126, 0.8%) and a delivery rate of 81% [44]. These positive findings were echoed in a retrospective cohort comparing patients who underwent adenomyomectomy vs. myomectomy via laparoscopic or open approach, with a live birth rate of 46 vs. 71%, $P = 0.076$ [46]. In patients whose endometrial cavity was entered intra-operatively, hysteroscopy 3 months later revealed 35% with stage I intrauterine synechiae, treated with adhesiolysis [46]. A retrospective series of all 22 pregnancies after adenomyomectomy performed by a single surgeon from 2011 to 2019 found four placental abnormalities, one case of uterine

rupture, and no hysterectomies [47]. Another retrospective cohort among infertility patients with both adenomyosis and endometriosis demonstrated a 12% incidence of placental abnormalities after a laparoscopic surgery to remove endometriosis and adenomyosis, though the type of excisional procedures were variable [48▪]. The addition of medical therapy with a GnRH modulator following surgical excision has not shown an improvement in live birth rate compared with surgical excision alone [49].

In conclusion, pregnancy appears safe following excisional procedures; however, it is not clear if particular excisional approaches improve reproductive outcomes or if a particular type of excision minimizes potential harms, such as abnormal placentation or uterine rupture.

ASSOCIATION OF ADENOMYOSIS AND ENDOMETRIOSIS

Endometriosis is the presence of ectopic endometrial glands and stroma outside of the uterine cavity and commonly presents with dysmenorrhea, pelvic pain, and infertility. There appears to be a link between the presence of endometriosis and adenomyosis. Additionally, adenomyosis appears to be associated with a greater number of deep infiltrating endometriotic lesions [50]. In patients with suspected or diagnosed endometriosis based on symptoms, imaging, and pathologic findings, concurrent adenomyosis has been found in 21–59% of patients [51▪,52▪].

In women with findings of endometriosis and infertility, the additional presence of adenomyosis appears to worsen fertility outcomes. In a long-term follow-up study after laparoscopic cystectomy for endometriosis, 40% of patients were diagnosed with concomitant adenomyosis by US criteria. In the 6 years following cystectomy, patients with adenomyosis had a significantly lower rate of successful pregnancy (25 vs. 47%, $P = < 0.05$) compared with patients without adenomyosis [53▪]. The type of adenomyosis (focal, diffuse, or adenomyoma) did not affect live birth rates in patients with endometriosis and adenomyosis following laparoscopy [48▪]. Women who were diagnosed with adenomyosis by ultrasound and underwent endometriosis surgery were found to have higher rates of infertility, more need for IVF treatment, and greater number of IVF cycles compared with women without ultrasound findings of adenomyosis [52▪]. Although co-occurring adenomyosis and endometriosis is associated with increased infertility and decreased live birth rate, additional prospective study is warranted to determine if treating adenomyosis medically or surgically in the setting of endometriosis and infertility improves fertility outcomes.

CONCLUSION

Adenomyosis causes dysmenorrhea and abnormal uterine bleeding, and is associated with infertility. TVUS and MRI during infertility evaluation can identify myometrial changes associated with adenomyosis with reasonable sensitivity and specificity, potentially avoiding more invasive tissue diagnosis. The lack of consensus for features required for imaging diagnosis creates challenges for interpreting studies that utilize different diagnostic criteria. Medical treatment with GnRH modulators may improve fertility among patients with adenomyosis undergoing IVF. Ablative and excisional treatment appear to be associated with low rates of complication, such as abnormal placentation; however, it is not known if these therapies improve reproductive outcomes. Future study utilizing in-vitro models can better understand the mechanisms of disease and provide specific targets for treatment [24]. Prospective trials can inform optimal medical and surgical management for uterine-sparing treatment of adenomyosis among women desiring fertility.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

1. Ferenczy A. Pathophysiology of adenomyosis. Hum Reprod Update 1998; 4:312–322.
2. ▪ Nirgianakis K, Kalaitzopoulos DR, Schwartz ASK, *et al.* Fertility, pregnancy and neonatal outcomes of patients with adenomyosis: a systematic review and meta-analysis. Reprod BioMed Online 2021; 42:185–206.

This systematic review and meta-analysis included 17 studies that included a control group (4 prospective and 13 retrospective), and provided fertility, pregnancy, and neonatal data for women with adenomyosis. No difference was seen in the live birth rate when all studies were combined; however, in women with adenomyosis, a short down-regulation protocol using GnRH-antagonist and agonist was associated with a lower clinical pregnancy rate (OR 0.34, 95% CI 0.20–0.57; $P < 0.0001$), higher miscarriage rate (OR 4.32, 95% CI 1.77–10.55; $P = 0.001$), and lower live birth rate (OR 0.19, 95% CI 0.09–0.42; $P < 0.0001$)

3. ▪ Cozzolino M, Tartaglia S, Pellegrini L, *et al.* The effect of uterine adenomyosis on IVF outcomes: a systematic review and meta-analysis. Reprod Sci 2022; doi: 10.1007/s43032-021-00818-6 [Epub ahead of print]

This systematic review and meta-analysis included 7738 patients from 22 studies (7 prospective cohorts and 15 retrospective cohorts) investigating reproductive outcomes among women with adenomyosis pursuing in vitro fertilization. Of the 9 studies that examined live birth weight, adenomyosis was associated with a lower live birth rate (OR 0.59, 95% CI 0.39-0.92, $P = 0.02$).

4. Huang Y, Zhao X, Chen Y, *et al.* Miscarriage on endometriosis and adeno-
■ myosis in women by assisted reproductive technology or with spontaneous conception: a systematic review and meta-analysis. Biomed Res Int 2020; 2020:4381346.

This review included 39 studies that evaluated miscarriage risk in 697 984 subjects with endometriosis or adenomyosis and underwent assisted reproductive technology or had spontaneous conception. Compared with women without adenomyosis, adenomyosis was associated with an increased miscarriage risk in women undergoing assisted reproductive technology OR 2.81, 95% CI (1.44–5.47), $I^2 = 64\%$,

5. Ono Y, Ota H, Takimoto K, *et al.* Perinatal outcomes associated with the
■ positional relationship between the placenta and the adenomyosis lesion. J Gynecol Obstet Hum Reprod 2021; 50:102114.

In this retrospective cohort including 20 women with adenomyosis, 11 women had evidence on ultrasound and/or MRI of placenta overlapping areas affected by adenomyosis. There was a 21.4% obstetric morbidity defined as a composite score including preterm delivery, fetal growth restriction, hypertensive disorder of pregnancy, placental malposition, oligohydramnios, gestational diabetes, and cesarean delivery.

6. Exacoustos C, Lazzeri L, Martire FG, *et al.* Ultrasound findings of adenomyosis
■■ in adolescents: type and grade of the disease. J Minim Invasive Gynecol 2021; 29:291.e1–299.e1.

This retrospective cohort demonstrated the presence of adenomyosis in adolescents, aged 12–20 years, based on ultrasound findings. Adenomyosis was categorized into focal, diffuse, or adenomyomas and was correlated with symptoms including amount and duration of menstrual bleeding, dysmenorrhea, chronic pelvic pain, dyspareunia, dyschezia, dysuria, and gastrointestinal symptoms.

7. Yu O, Schutze-Rath R, Grafton J, *et al.* Adenomyosis incidence, prevalence and treatment: United States population-based study 2006-2015. Am J Obstet Gynecol 2020; 223:94.e1–94.e10.
8. Loring M, Chen T, Isaacson KB. A systematic review of adenomyosis: it is time
■ to reassess what we thought we knew about the disease. J Minim Invasive Gynecol 2021; 28:644–655.

This systematic review included 16 studies constituted of randomized controlled trials and observational studies that utilized a variety of diagnostic methods including ultrasound, MRI, and histology. The prevalence of adenomyosis in symptomatic women ranged from 20 to 88.8% with an average of 30 to 35%.

9. Bourdon M, Santulli P, Oliveira J, *et al.* Focal adenomyosis is associated with
■ primary infertility. Fertil Steril 2020; 114:1271–1277.

This single institution, retrospective, cross-sectional study included reproductive aged women who underwent preoperative MRI and surgery for benign gynecologic indications including 248 women with adenomyosis and 248 women without adenomyosis. Adenomyosis was associated with primary infertility with an adjusted OR of 1.9, 95% CI 1.1–1.3, with strong association between primary infertility and focal adenomyosis of the outer myometrium.

10. Abu Hashim H, Elaraby S, Fouda AA, Rakhawy ME. The prevalence of adenomyosis in an infertile population: a cross-sectional study. Reprod Biomed Online 2020; 40:842–850.
11. Movilla P, Morris S, Isaacson K. A systematic review of tissue sampling techniques for the diagnosis of adenomyosis. J Minim Invasive Gynecol 2020; 27:344–351.
12. Van den Bosch T, Dueholm M, Leone FPG, *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; 46:284–298.
13. Da Silva JR, Andres MP, Leite APK, *et al.* Comparison of sensitivity and
■ specificity of structured and narrative reports of transvaginal ultrasonography for adenomyosis. J Minim Invasive Gynecol 2021; 28:1216–1224.

This retrospective study included 192 women (45 with adenomyosis and 147 controls) who underwent hysterectomy and compared preoperative TVUS findings and histologic sample from hysterectomy. Narrative reports (from original TVUS report) and structured report (two radiologists were asked to review the images independently) showed sensitivities of 31 vs. 69–84% and specificities of 91 vs. 28–31%, respectively. Whenever using two US features instead of one, there was better sensitivity and specificity for the structured reports.

14. Zannoni L, Ambrosio M, Raimondo D, *et al.* Question mark sign and transvaginal ultrasound uterine tenderness for the diagnosis of adenomyosis. J Ultrasound Med 2020; 39:1405–1412.
15. Chapron C, Vannuccini S, Santulli P, *et al.* Diagnosing adenomyosis: an integrated clinical and imaging approach. Hum Reprod Update 2020; 26:392–411.
16. Liu L, Li W, Leonardi M, *et al.* Diagnostic accuracy of transvaginal ultrasound
■ and magnetic resonance imaging for adenomyosis: systematic review and meta-analysis and review of sonographic diagnostic criteria. J Ultrasound Med 2021; 40:2289–2306.

This systematic review included 32 studies to evaluate the accuracy of imaging for the diagnosis of adenomyosis compared with hysterectomy samples (26 studies looking at ultrasound, 3 looking at MRI and 3 looking at both ultrasound and MRI findings). The addition of ultrasound technologies, such as 3D TVUS, elastography, and Doppler studies and its effect on diagnostic accuracy was also evaluated. TVUS was found to be comparable in the diagnosis of adenomyosis compared with MRI.

17. Marques ALS, Andres MP, Mattos LA, *et al.* Association of 2D and 3D
■ transvaginal ultrasound findings with adenomyosis in symptomatic women of reproductive age: a prospective study. Clinics (Sao Paulo) 2021; 76:e2981.

In a prospective study of 78 women w/abnormal uterine bleeding, pelvic pain, and/or infertility who underwent 2D and 3D TVUS, 3D TVUS was used to evaluate the junctional zone. Forty-three women (55%) were diagnosed with adenomyosis by MUSA criteria. Women with adenomyosis compared with women without adenomyosis were older and more likely to have abnormal uterine bleeding and dysmenorrhea.

18. Sasaran V, Turdean S, Gilga M, *et al.* Value of strain-ratio elastography in the
■ diagnosis and differentiation of uterine fibroids and adenomyosis. J Pers Med 2021; 11:824.

In a prospective pilot study of 79 women when underwent hysterectomy, 25 were diagnosed with adenomyosis and 53 were diagnosed with fibroids. TVUS with elastography was performed less than 24 h prior to surgery. Diagnostic sensitivity and specificity was better for fibroids compared with adenomyosis (91 vs. 86 and 96 and 91%, respectively), and higher elastography stiffness was appreciated in adenomyosis compared to fibroids

19. Sam M, Raubenheimer M, Manolea F, *et al.* Accuracy of findings in the diagnosis of uterine adenomyosis on ultrasound. Abdom Radiol (NY) 2020; 45:842–850.
20. Zanolli NC, Cline BC, Befera NT, Martin JG. Diagnostic accuracy of clinically
■ reported adenomyosis on pelvic ultrasound and MRI compared to surgical pathology. Clin Imaging 2022; 82:117–120.

This retrospective study of 180 women with both preoperative MRI and TVUS who underwent a hysterectomy for benign indications noted overall lower than previous reported clinical diagnostic accuracy for both MRI and TVUS when adenomyosis was not explicitly evaluated for on imaging.

21. Rees CO, Nederend J, Mischi M, *et al.* Objective measures of adenomyosis on
■ MRI and their diagnostic accuracy—a systematic review & meta-analysis. Acta Obstet Gynecol Scand 2021; 100:1377–1391.

In a systematic review of 80 studies assessing accuracy of MRI imaging findings for the diagnosis of adenomyosis compared with histologic diagnosis of adenomyosis, MRI had an overall pooled sensitivity of 60% and specificity of 96%.

22. Tellum T, Matic G, Dormagen J, *et al.* Diagnosing adenomyosis with MRI: a prospective study revisiting the junctional zone thickness cutoff of 12 mm as a diagnostic marker. Eur Radiol 2019; 29:6971–6981.
23. Kobayashi H, Matsubara S. A classification proposal for adenomyosis based on magnetic resonance imaging. Gynecologic and obstetric investigation. Gynecol Obstet Invest 2020; 85:118–126.
24. Gnecco JS, Brown AT, Kan EL, *et al.* Physiomimetic models of adenomyosis. Semin Reprod Med 2020; 38(2–03):179–196.
25. Zhai J, Vannuccini S, Petraglia F, Giudice LC. Adenomyosis: mechanisms and pathogenesis. Semin Reprod Med 2020; 38:129–143.
26. Munro M. Uterine polyps, adenomyosis, leiomyomas, and endometrial receptivity. Fertil Steril 2019; 111:629–640.
27. Xie T, Xu X, Yang Y, *et al.* The role of abnormal uterine junction zone in the
■ occurrence and development of adenomyosis. Reprod Sci 2021; doi: 10.1007/s43032-021-00684-2 [Epub ahead of print]

This review of normal and abnormal junctional zone contractility discusses proposed mechanisms of smooth muscle cell dysfunction in adenomyosis. Abnormal tissue healing, vascular proliferation, and inflammatory pathways may contribute to the smooth muscle response to ectopic endometrial glands and stroma.

28. Peng Y, Jin Z, Liu H, Xu C. Impaired decidualization of human endometrial
■ stromal cells from women with adenomyosis. Biol Reprod 2021; 104:1034–1044.

Markers of decidualization were reduced in tissue samples from 8 patients with adenomyosis compared with 12 patients without adenomyosis. Protein expression and mRNA necessary for decidualization of endometrium were reduced in patients with adenomyosis.

29. Kay N, Huang CY, Shiu LY, *et al.* TGF-(1 neutralization improves pregnancy
■ outcomes by restoring endometrial receptivity in mice with adenomyosis. Reprod Sci 2021; 28:877–887.

In a mouse model of adenomyosis, implantation rates were improved with anti-TGF-β1 treatment.

30. Neal S, Morin S, Werner M, *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; 56:611–617.

This prospective cohort of women with infertility and adenomyosis undergoing frozen embryo transfer demonstrated no difference in reproductive outcomes. Limitations of the study include broad ultrasound criteria requiring only one of seven features for diagnosis of adenomyosis: global uterine enlargement, asymmetric myometrium, heterogeneous myometrium, irregular junctional zone, myometrial cysts, fan-shaped shadowing, and myometrial lesions.

31. Lan J, Wu Y, Wu Z, *et al.* Ultra-Long GnRH agonist protocol during IVF/ICSI
■ improves pregnancy outcomes in women with adenomyosis: a retrospective cohort study. Front Endocrinol (Lausanne) 2021; 12:609771.

In this retrospective cohort including women with adenomyosis undergoing IVF and ICSI, there were 212 women with ultra-long GnRH-agonist protocol and 116 women with long GnRH-agonist protocol as pretreatment. Among the cohort of women with diffuse adenomyosis, ultra-long GnRH-agonist protocol was associated with higher clinical pregnancy rate and live birth rate.

32. ■ Hou X, Xing J, Shan H, *et al.* The effect of adenomyosis on IVF after long or ultra-long GnRH agonist treatment. Reprod Biomed Online 2020; 41:845–853.
This retrospective cohort included women with adenomyosis compared with women with tubal factor infertility undergoing first cycle of IVF treatment. Women with adenomyosis underwent ultra-long GnRH agonist protocol (at least 3 months of triptorelin 3.75 mg i.m.) or long GnRH agonist protocol (short acting triptorelin daily starting in the mid-luteal phase of prior cycle) whereas women with tubal factor infertility underwent long GnRH agonist protocol.

33. ■ Wu Y, Huang J, Zhong G, *et al.* Long-term GnRH agonist pretreatment before frozen embryo transfer improves pregnancy outcomes in women with adenomyosis. Reprod Biomed Online 2021; 44:380–388.
This retrospective cohort included 537 women with adenomyosis undergoing IVF with fresh vs. frozen transfer and with GnRH long or ultra-long pretreatment. There were higher live birth rates with frozen embryo transfer and long-term GnRHa pretreatment.

34. ■ Li M, Xu L, Zhao H, *et al.* 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.
This retrospective cohort included 341 patients 45 years or less with adenomyosis and undergoing IVF with GnRH-agonist pretreatment compared with hormonal replacement to prepare the endometrium. There was no significant difference in clinical pregnancy rate (40.63 vs. 42.5%, $P = 0.72$) and live birth rate (23.75 vs. 23.75%, $P = 0.74$) for study and control groups, respectively.

35. ■ Chen M, Luo L, Wang Q, *et al.* Impact of gonadotropin-releasing hormone agonist pretreatment on the cumulative live birth rate in infertile women with adenomyosis treated with IVF/ICSI: a retrospective cohort study. Front Endocrinol (Lausanne) 2020; 11:318.

36. ■ Li X, Pan N, Zhang W, *et al.* Association between uterine volume and pregnancy outcomes in adenomyosis patients undergoing frozen-thawed embryo transfer. Reprod Biomed Online 2021; 42:384–389.
In a retrospective cohort of women with adenomyosis undergoing frozen–thawed embryo transfer with pretreatment with GnRH-agonist, uterine volume was measured. After controlling for confounders with logistic regression, uterine volume using a cutoff of 98.81 cm^3 was associated with a decreased live birth rate and increased miscarriage rate.

37. ■ Serres-Cousine O, Kuijper FM, Curis E, Atashroo D. Clinical investigation of fertility after uterine artery embolization. Am J Obstet Gynecol 2021; 225:403e1–403e22.
In a retrospective cohort of 398 patients, there were 44 women with adenomyosis and fibroids and 21 women with pure adenomyosis who underwent uterine artery embolization. Of the 18% of patients who were diagnosed with adenomyosis, there was a reduced clinical success rate of 86% (OR 0.47, 95% CI 0.23–0.97, $P = 0.0414$) compared with 93% without adenomyosis and a reduced obstetrical success rate of 53% (OR 0.64, 95% CI 0.29–1.44, $P = 0.3008$) vs. 64% without adenomyosis though this was not statistically significant.

38. ■ Ma J, Brown B, Liang E. Long-term durability of uterine artery embolisation for treatment of symptomatic adenomyosis. Aust N Z J Obstet Gynaecol 2021; 21:290–296.
This cross-sectional study of 104 women with initial symptom relief after uterine artery embolization included follow-up questionnaires assessing symptoms and quality of life. At a mean duration of 52 months after treatment, 82 of 91 noted persistent relief though 53 of 91 women began menopause during the interval from treatment to posttreatment assessment.

39. Lin XL, Hai N, Zhang J, *et al.* Comparison between microwave ablation and radiofrequency ablation for treating symptomatic uterine adenomyosis. Int J Hyperthermia 2020; 37:151–156.

40. ■ Liu L, Wang T, Lei B. Image-guided thermal ablation in the management of symptomatic adenomyosis: a systematic review and meta-analysis. Int J Hyperthermia 2021; 38:948–962.
This systematic review and meta-analysis included 15 908 women and assessed symptom relief, uterine volume, adverse event rates, and pregnancy rates following high-intensity focused ultrasound, percutaneous microwave ablation, and radiofrequency ablation. The highest pregnancy rates were reported after radiofrequency ablation; however, there was a lower average age in the single included study that reported pregnancy rates after radiofrequency ablation.

41. Nam JH. Pregnancy and symptomatic relief following ultrasound-guided transvaginal radiofrequency ablation in patients with adenomyosis. J Obstet Gynaecol Res 2020; 46:124–132.

42. Marques ALS, Andres MP, Kho RM, Abrão MS. Is high-intensity focused ultrasound effective for the treatment of adenomyosis? A systematic review and meta-analysis. J Minim Invasive Gynecol 2020; 27:332–343.

43. Huang YF, Deng J, Wei XL, *et al.* A comparison of reproductive outcomes of patients with adenomyosis and infertility treated with high-intensity focused ultrasound and laparoscopic excision. Int J Hyperthermia 2020; 37:301–307.

44. Mikos T, Lioupis M, Anthoulakis C, Grimbizis GF. The outcome of fertility-sparing and nonfertility-sparing surgery for the treatment of adenomyosis. A systematic review and meta-analysis. J Minim Invasive Gynecol 2020; 27:309–331.

45. Osada H. Uterine adenomyosis and adenomyoma: the surgical approach. Fertil Steril 2018; 109:406–417.

46. Hlinecka K, Mara M, Boudova B, *et al.* Comparison of clinical and reproductive outcomes between adenomyomectomy and myomectomy. J Minim Invasive Gynecol 2021; 29:392–400.

47. Kwack JY, Lee SJ, Kwon YS. Pregnancy and delivery outcomes in the women who have received adenomyomectomy: performed by a single surgeon by a uniform surgical technique. Taiwan J Obstet Gynecol 2021; 60:99–102.

48. ■ Shi J, Dai Y, Zhang J, *et al.* 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.
This retrospective study included 176 women with infertility and endometriosis and adenomyosis (diagnosed by >2 MUSA features) who underwent laparoscopic surgical treatment. One hundred and thirty-five (74%) of patients underwent IVF, 70 patients (52%) had live births, and 35 (19%) failed to conceive at all.

49. Wang PH, Liu WM, Fuh JL, *et al.* Comparison of surgery alone and combined surgical-medical treatment in the management of symptomatic uterine adenomyoma. Fertil Steril 2009; 92:876–885.

50. Marcellin L, Santulli P, Bourdon M, *et al.* Focal adenomyosis of the outer myometrium and deep infiltrating endometriosis severity. Fertil Steril 2020; 114:818–827.

51. ■ Capezzuoli T, Vannuccini S, Fantappie F, *et al.* Ultrasound findings in infertile women with endometriosis: evidence of concomitant uterine disorders. Gynecol Endocrinol 2020; 36:808–812.
This retrospective study included a cohort of 419 women with infertility and US evidence of endometriosis for concomitant uterine disorders. Using MUSA criteria, US diagnosis of fibroids was found in 3.1% of patients and adenomyosis was found in 21.2%.

52. ■ Decter D, Arbib N, Markovitz H, *et al.* Sonographic signs of adenomyosis in women with endometriosis are associated with infertility. J Clin Med 2021; 10:2355.
In a retrospective study of 402 women who were referred to an endometriosis center, 244 (60.7%) underwent surgical treatment for endometriosis and 158 (39.3%) underwent conservative management. Adenomyosis was diagnosed by US features. Any feature of adenomyosis seen on United States was present in 292 of 402 (73%) of patients, with more than three ultrasound features seen in 259 of 402 (64%) of patients and more than five ultrasound features seen in 156 of 402 (39%) of patients. In women who underwent surgical treatment, more than five ultrasound features of adenomyosis was associated with higher rates of infertility, IVF treatments, and higher number of IVF cycles.

53. ■ Sun TT, Li XY, Shi JH, *et al.* Clinical features and long-term outcome after laparoscopic surgery in patients co-existing with endometriosis and adenomyosis. Front Med (Lausanne) 2021; 8:696374.
In this retrospective study of 358 patients who underwent laparoscopic cystectomy for endometriosis, 142 (39.7%) were found to have concomitant adenomyosis and 216 (60.3%) did not have adenomyosis by ultrasound diagnosis (≥3 features). There was no difference in prevalence of infertility prior to surgery between the two groups, following surgery 75% (107/142) of patients with adenomyosis had failed pregnancy vs. 53% (114/216) in the nonadenomyosis group; overall live birth rate 97% for both groups.