

Adenomyosis and Its Effect on Reproductive Outcomes

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Abstract

Background: Adenomyosis was historically diagnosed on histological examination of the uterus after hysterectomy in older parous women. However, it is becoming more prevalent in women wishing to conceive due to the social trend towards delaying fertility alongside improved imaging techniques. This has led to a dilemma regarding whether adenomyosis should be actively diagnosed and treated in the fertility setting.

This review aims to present the current controversies in the evidence with regards to (i) prevalence of adenomyosis in the sub-fertile population (ii) its effects on fertility, (iii) its effects on assisted reproduction techniques (ART), (iv) its effects on obstetric outcomes, (v) the efficacy of fertility sparing treatments in the sub-fertile population.

Methods: Searches of Medline and Pubmed were searched independently by the reviewers using the key words 'adenomyosis', 'adenomyoma', 'reproductive outcomes', 'obstetric outcomes', 'miscarriage', 'ART', 'assisted reproductive technique'. Animal studies were excluded and studies were limited to the English language.

Results: The prevalence of adenomyosis in the sub-fertile population is difficult to determine due to a lack of robust epidemiological studies. There are conflicting and variable reports in the literature regarding the effects of adenomyosis on fertility and ART with the majority of studies supporting no association. There is some evidence to suggest that the condition does increase the incidence of preterm labour and premature rupture of membranes once pregnancy is achieved. Most of the fertility sparing treatment options for adenomyosis are cited in case series and reports from limited populations, hence their true effect on conception remains unclear.

Conclusion: Further epidemiological studies are needed to evaluate the prevalence and impact of adenomyosis in the sub-fertile population. Currently the existing literature on the effect of the disease on fertility is inconclusive; hence, actively diagnosing and treating the condition is debatable in women wishing to conceive. However, once pregnancy is achieved, the evidence suggests a detrimental effect on delivery rate, with an increased risk of miscarriage and preterm labour. There is some success seen in treating women undergoing assisted reproduction. Clinicians could consider a long course of pituitary down regulation prior to ART in appropriately informed sub-fertile women.

Keywords: Adenomyosis; Myometrial cysts

Introduction

Adenomyosis is a benign condition of the uterus that is characterised by the presence of endometrial tissue within the myometrium [1]. It commonly presents in the fourth decade of life with secondary dysmenorrhoea, menorrhagia, and menstrual irregularity. The condition has an association with other gynaecological pathologies including endometriosis, fibroids, endometrial polyps and endometrial adenocarcinoma. This makes its clinical significance difficult to separate and interpret from these other common gynaecological conditions. Clinicians should however consider adenomyosis as part of their differential diagnoses, if faced with patients who do not respond to the conventional treatment for painful and heavy periods.

Adenomyosis is thought to arise from abnormal invagination of the endometrium into a predisposed myometrium or traumatised endometrial-myometrial interface [2]. Risk factors include increased parity, pregnancy and surgical curettage of the gravid uterus. The process of invagination has been theorised to entail initiation by mechanical insult in the form of either abnormal peristaltic function or structural abnormalities in the organization of myometrial tissue [3-5], either to the endometrium, the endometrial-myometrial interface, or the myometrium [6]. It is postulated that after the initial insult, the pathological process is propagated by some combination of favourable hormonal and immunological conditions which occur alongside cell adhesion abnormalities [7-12].

Studies have focused on different aspects of the theory of invagination and have conceptualized the relationship between these factors and the nature of the endometrial migration differently. The process has not yet been reconciled but the evidence suggests that it is

an immune-hormonal aberration of normal cyclical uterine changes, possibly due to underlying gene dysregulation.

Although the actual clinical significance of the condition is debatable, there is evidence to suggest that adenomyosis leads to an increased risk of miscarriage, pre-term labour and subfertility [13]. The mechanism of this is currently poorly understood.

In the fertility setting, patients are presenting in their early 40s for treatment and therefore adenomyosis is becoming more prevalent and relevant in this population. There is sparse data on its specific effects on conception, Assisted Reproduction Techniques (ART) and obstetric/perinatal outcome. This presents a dilemma for clinician managing this group of women whose fertility may already be compromised by advanced age and concomitant endometriosis. It also highlights whether conditions such as adenomyosis may be contributing to the underlying pathology in women who fall into the "unexplained infertility" group of patients.

In this review we present the current controversies in the evidence

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with regards to (i) diagnosis, (ii) prevalence of adenomyosis in the sub-fertile population (iii) its effects on fertility, (iv) its effects on ART, (v) its effects on obstetric outcomes, (vi) the efficacy of fertility sparing treatments in the sub-fertile population.

Diagnosis

Historically the diagnosis of adenomyosis was made histologically on uteri removed at the time of hysterectomy [14]. However, with marked improvement in imaging techniques, both Transvaginal Ultrasound (TVU) and Magnetic Resonance Imaging (MRI) are also good diagnostic tools (Tables 1 and 2). Despite this advancement, there are currently no internationally agreed criteria for diagnosing the condition both radiologically and on histology examination, nor is there an established, standardised method of grading severity. This makes estimating the prevalence of adenomyosis in the general population difficult but extrapolating from histological examination of hysterectomy samples, it ranges from 5-70% [15].

The current consensus is that MRI and TVUS are both accurate modalities for diagnosing adenomyosis though some studies suggest that MRI has a marginal advantage [16,28]. Dueholm cites increased specificity compared with TVUS but equivalent sensitivity and also reported good accuracy with TVUS but only in women with clinically suspected disease [17,27]. Other studies indicate that TVUS offers a comparable level of accuracy with statistically insignificant differences in sensitivity and specificity [29]. A large meta-analysis comparing TVUS with histopathological diagnosis concluded TVUS to be an accurate mode of diagnosis with an overall sensitivity and specificity in symptomatic patients of 84.3% and 82.3% respectively [30]. Most studies included in the meta-analysis used myometrial heterogeneity or myometrial cysts, which have been identified as the most sensitive (88%) and specific (98%) signs respectively [18]. Exacoustos suggests that 3D TVUS is superior to 2D TVUS, with an increase in accuracy from 83% to 89% [8,18]. One synthesis advocates TVUS as a primary

screening modality, with MRI offering definitive diagnosis [31]. MRI has also been identified as offering more diagnostic consistency even with the presence of fibroids [28], supporting its function as a more definitive modality. TVUS is regarded as a sound screening and valid diagnostic tool in the first instance, where MRI may not be freely available to financially viable.

What is the prevalence of adenomyosis in the sub-fertile population?

There is limited literature on the epidemiology of adenomyosis associated with sub-fertility and it is difficult to establish a cause-effect relationship between the two variables. To date there is only one study that has looked at the prevalence of adenomyosis in the sub-fertile population [32]. The investigators studied the prevalence of MRI diagnosed adenomyosis in 227 women attending a fertility clinic. They also stratified the women into laparoscopically diagnosed endometriosis and adenomyosis versus those without endometriosis. The prevalence of adenomyosis alone was evaluated as 28%. Other studies [33,34] have stated a prevalence of 52.5% and 53.8% respectively in women presenting outside the fertility setting namely with longstanding dysmenorrhoea. These estimations are confounded by the lack of international consensus regarding the MRI criteria for diagnosing adenomyosis and the heterogeneity of the populations studied. The strong association between adenomyosis and endometriosis is another confounding factor, as it is difficult to delineate whether they are the same disease or separate entities.

The effect of Adenomyosis on natural fertility

There is no data to determine the effect of adenomyosis on natural conception; however, some studies suggest mechanisms of reduced fertility, most notably abnormal sperm transport systems [35]. Kunz posits that impairment of sperm transport is the most likely cause of reduced fertility on the basis that dysperistalsis reduces "uterine transport capacity" [32] and arises due to the disruption of the myometrial architecture. Kunz also found the posterior junctional zone to be thicker in women with fertile partners compared to women with infertile partners, suggesting that adenomyotic junctional zone thickening is implicated in these women's infertility [32]. Similarly, Kissler compared women with endometriosis who additionally had either focal or diffuse adenomyosis; whilst the focal group demonstrated reduced uterotubal transport, the diffuse group demonstrated a failure of uterotubal transport thus providing a mechanism for the previously unclear association [33]. Reduced uterotubal transport function is an important cause of infertility as the pregnancy rate following negative hysterosalpingo sonography (HSSG) was found to be 10% [36].

The effect of Adenomyosis on ART

The effect of adenomyosis on ART remains conflicting although most studies overall suggest that there is no detrimental impact. The largest systematic review to date by Maheshwari et al. [37] was inconclusive regarding the effect of adenomyosis on ART suggesting that further robust studies are needed to determine if there is an association. The most recent studies to postdate Maheshwari et al both report significant findings regarding lower pregnancy rates in adenomyotic patients.

Most of the evidence has been generated from small case-control or retrospective studies looking at the effect of adenomyosis on In vitro fertilisation (IVF)/Intracytoplasmic sperm injection (ICSI) success in particular the implantation and miscarriage rates.

Costello et al. [38] found no difference in implantation and

Diagnosing Adenomyosis	
Clinical features	Uterine enlargement Dysmenorrhoea Menorrhagia
Histopathology	Uterine enlargement [15] Globular or asymmetric uterus Dense, irregularly fasciculated, unlimited myometrium with 0.5-10mm cavities [16] Ectopic endometrial tissue > 2.5mm [16]
Trans-abdominal Ultrasound	Uterine enlargement No evidence of leiomyoma And/or presence of myometrial cyst [16]
2D TVUS	Myometrial cyst [16-19] Poorly delineated heterogeneous myometrium [13-23] Subendometrial linear striations [22-24] Subendometrial echogenic nodules [24] Myometrial antero-posterior asymmetry [22,23] Globular uterus [16,22,23] Absent flow or straight vessels within hypertrophic myometrium on colour Doppler [16]
3D TVUS	$JZ_{off} \geq 4mm$ [18] JZ infiltration and distortion [18]
T2-weighted MRI	Large, regular, asymmetric uterus Maximal junctional zone $\geq 12mm$ and/or ill-defined low signal area [16,25,26] Ratio $\frac{JZ_{max}}{JZ_{min}} > 40\%$ [16] $JZ_{off} > 5mm$ [27] High-intensity myometrial foci [16,25-27]

¹ Maximal difference between the thickest and thinnest junctional zone

² Maximal junctional zone (JZ) thickness to myometrial thickness ratio

Table 1: The diagnostic features of Adenomyosis.

Authors	Type	Population	Main Findings
Yan L et al. [44]	Retrospective matched cohort study	77 patients with adenomyosis of 10,268 undergoing hyperstimulation and IVF/ICSI matched with adenomyosis matched to 77 adenomyosis-free patients.	Patients with adenomyosis had a nonsignificant trend toward a lower clinical pregnancy rate (19% vs 82.4%) and a significantly higher miscarriage rate. Significantly lower delivery rate in the adenomyosis group.
Salim et al. [43]	Prospective, observational screening study	19 patients with adenomyosis with a control group of 256 patients First cycle IVF/ICSI following short antagonist protocol (Buserelin)	Clinical pregnancy rate 22.2% vs. 47.2% Ongoing pregnancy rate 11.1% vs. 45.9% First trim. miscarriage rate 50.0% vs. 2.8%
Thalluri V, Tremellen KP [42]	Retrospective cohort study	38 patients with adenomyosis with a control group of 175 patients. First cycle IVF following ultra-long antagonist down-regulation for 3 months.	Viable clinical pregnancy rate 23.6% versus 44.6%
Tremellen K, Russell P [41]	Case series	4 patients Ultra-long downregulation.	Prior to adenomyosis treatment the group had an average of 15 embryos transferred with no successful pregnancies; following treatment all the women were pregnant within 2 cycles of IVF.
Costello et al. [38]	Retrospective cohort study	37 patients with adenomyosis with a control of 201 patients. Single stimulated cycle of IVF/ICSI following long GnRH protocol.	No difference in live birth rate, ovarian response, embryological parameters or clinical outcomes between groups. Type 2 study error regarding effect on live birth rates.
Jose A. Martinez-Conejero [40]	Retrospective matched cohort study	144 patients with ovarian endometriosis of 443 undergoing IVF and oocyte donation with a control of 147 patients.	Miscarriage rate Adenomyosis 13.1% Adenomyosis + endometriosis 6.1% Control 7.2% Term pregnancy Significantly lower in adenomyosis alone (26.8%) than adenomyosis + endometriosis (38.0%) or control (37.1%).
Mijatovic V [39]	Restrospective	20 patients with adenomyosis and endometriosis with an endometriosis only control of 54 patients. IVF/ICSI following long GnRH-agonist	No significant difference in fertility rate, implantation rate, miscarriage rate, ectopic rate or ongoing pregnancy rate.

Table 2: Studies exploring adenomyosis in relation to ART outcome.

miscarriage rates in their retrospective cohort study of 201 women with adenomyosis undergoing either IVF/ICSI. Mijatovic et al. [39] also confirmed this finding in a similarly designed study of 74 patients. However they included women with surgically diagnosed endometriosis in their cohort which confounds the association. Their patients also had a prolonged course of down regulation with Gonadotropin Releasing Hormone (GnRH) agonists which are known to be a successful treatment for adenomyosis. Hence it is debateable as to whether these findings are entirely robust. Moreover it is difficult to ascertain the true effect of adenomyosis as it may be partially treated by this intervention and hence another confounding factor.

Conversely, Martinez-Conjero et al. [40] found women with adenomyosis had a higher miscarriage rate (13.1% vs 7.2%) in their retrospective cohort study of 443 women undergoing IVF with oocyte donation. In their case series of 4 women with adenomyosis and recurrent implantation failure, Tremellen and Russell [41] also found a higher rate of miscarriage. However they employed a course of ultra-long downregulation prior to IVF and found all their women became pregnant with no implantation failures.

More recently, Thalluri and Tremellen [42] identified a decreased clinical pregnancy rate (23.6% vs 44.6%) when comparing the adenomyosis group to the non-adenomyosis group, which was statistically significant after adjustment for maternal age and duration of infertility. Similarly, Salim et al. [43] offers a 275 patient prospective observational screening study which identified a reduced clinical pregnancy rate (22.2% vs 47.2%) and ongoing pregnancy rate (11.1% vs 45.9%) in addition to an increased first trimester miscarriage rate (50.0% vs 2.8%) although there was no significant difference in implantation failure. The study used a short course of pituitary downregulation commenced in the mid-luteal phase.

A recent large retrospective cohort study also reported a

significantly lower delivery rate in an adenomyosis group [44]. In this study, patients were stimulated by long GnRH agonist, short agonist or antagonist; however, the sample was too small to comment on the significance of the long protocol.

Niu et al.[33] found a long course of downregulation to significantly improve the clinical pregnancy rate, ongoing pregnancy rate and implantation rate in patients with adenomyosis. Tremellen and Russell [29] offer a pathophysiological basis with increased endometrial macrophage infiltrates identified on biopsy in women with untreated adenomyosis contributing to implantation failure. Khan furthermore found that long course downregulation reduces these macrophage infiltrates [34].

The largest and best-controlled studies on the effect of adenomyosis on ART suggest a detrimental impact on miscarriage and ongoing pregnancy rates; however, emerging evidence suggests that long course down regulation may ameliorate this process.

The effect of adenomyosis on obstetric outcomes

The largest study (45) looking at adenomyosis in 2138 pregnant women found a higher incidence of preterm labour (odds ratio 1.84) and premature rupture of membrane (PROM) (odds ratio 1.98) in the cohort with the disease. The mechanism of this association is unclear.

There are also several case reports that describe an increased risk of uterine rupture and atony in pregnant women with adenomyosis [45,46].

The efficacy of fertility sparing treatments for adenomyosis in the sub-fertile population

There are various treatment options for subfertile women with adenomyosis, described in the literature ranging from insertion of danazol loaded intrauterine device, the use of GnRH agonists to surgical

techniques. However the evidence is limited to case reports and series of small patient numbers with their inherent publication bias.

Two case series comprising 39 patients with adenomyosis desiring fertility who used a danazol loaded intrauterine device or vaginal ring report a combined pregnancy rate of 41% [47,48].

The use of GnRH agonists has been evaluated in 3 small case series comprising of a total of 7 patients in whom pregnancy was achieved in 6, within 24 months of discontinuing the therapy[49-51].

Conservative surgery comprises of excising the adenomyotic tissue through hysteroscopic techniques, laparoscopically or by laparotomy and to date there are 3 case series that have evaluated this approach. The overall live birth rate from these studies was 36.2% (21 of 58 patients) [52-54].

Wang et al. compared conservative surgery with subsequent GnRH agonist use against a control group of GnRH agonist alone. In the 65 patient recruited the live birth rates following conservative surgery versus GnRH use were found to be 32.1% and 8% respectively [55].

Uterine artery embolization is emerging as a promising minimally-invasive procedure for the treatment of symptomatic fibroids and adenomyosis [30]. There are numerous studies highlighting major improvements to menorrhagia and patient satisfaction alongside reduction in hysterectomy rates. It has also been demonstrated that successful pregnancy may occur following UAE although placentation may be adversely affected[56]. Studies have not differentiated between adenomyosis and fibroids. Kim et al. looked at 94 patients undergoing UAE for fibroids and adenomyosis [57]. Of the three patients with adenomyosis who desired pregnancy, all three were successful; however, one woman delivered at 34 weeks with premature rupture of membranes with a small for gestational age neonate. There are currently no randomised controlled trials aimed at evaluating the different treatment options and hence no particular option can be advocated based on the existing pool of data.

Discussion

In light of an increasing aging reproductive population and improved imaging techniques, adenomyosis will present in a higher proportion of the future sub-fertile population. Clinicians need to be aware of adenomyosis and its effect on reproductive outcomes. Whilst the literature is inconclusive as to the management of these women, adenomyosis must be actively considered as a differential for unexplained fertility.

The pathophysiology of adenomyosis as an integrated process isn't fully understood although genetic, immunological and hormonal components have been identified. These processes have implications for fertility but the clinical ramifications have not been ascertained. The majority of studies are poorly designed, comprised of small numbers and therefore a definitive conclusion with regards to the effect on fertility is not possible.

Although imaging of adenomyosis has improved, there is no internationally-agreed classification to confirm diagnoses; therefore, the exact prevalence from an infertility population cannot be determined. In order to reduce bias, there also needs to be standardisation of the radiological/histological diagnostic criteria being used to determine the condition so that data is comparable. There is evidence to suggest that adenomyosis can be treated medically with preservation of fertility and the success rates following ART are encouraging.

Further work through good quality epidemiological studies is also

needed to quantify the impact of adenomyosis on fertility and evaluate the efficacy of treatment and ART.

Good Practice Points

1. Adenomyosis should be considered as a differential diagnosis in older women with unexplained infertility
2. In older women with unexplained infertility, particularly on negative HSSG, an MRI should be considered
3. Clinicians should be aware that adenomyosis affects reproductive outcomes and be receptive to emerging evidence
4. Once adenomyosis is diagnosed radiologically, clinicians should counsel women regarding the diversity of literature in terms of ART outcomes
5. Women who achieve pregnancy should be informed of potentially increased miscarriage rate and decreased ongoing pregnancy rate
6. In appropriately informed sub-fertile women, clinicians may consider offering long course pituitary downregulation prior to ART

Conclusion

Until the literature becomes clearer and more robust, there is no strong evidence to suggest that clinicians should actively diagnose and treat adenomyosis in women seeking fertility treatments. However they should be aware of its increasing existence in older women wishing to conceive and individualise care according to their overall reproductive health needs. Once pregnancy is achieved, the evidence suggests a detrimental effect on delivery rate, with an increased risk of miscarriage and preterm labour. Clinicians may therefore consider offering a long course of pituitary downregulation prior to ART in appropriately informed sub-fertile women.

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