Adenomyosis and subfertility: a systematic review of prevalence, diagnosis, treatment and fertility outcomes

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BACKGROUND: Uterine adenomyosis was initially thought to be found only in parous women, and final diagnosis was made at histology after hysterectomy. With better imaging techniques and with women attending clinics at older ages, adenomyosis is diagnosed with increasing frequency in women attending infertility clinics. A dozen conservative interventions have been advocated, with variable reports of their impact on fertility. This presents a dilemma for clinicians managing such patients. Hence, this systematic review of adenomyosis was performed to determine (i) the prevalence in a subfertile population, (ii) the accuracy of diagnostic tests, (iii) the efficacy of fertility sparing treatment options and (iv) the reproductive and obstetric/perinatal outcomes in women with adenomyosis.

METHODS: Systematic searches of various databases were performed independently by two reviewers, and data were extracted according to predefined criteria by two reviewers.

RESULTS: There is little data on the epidemiology of adenomyosis associated with subfertility. Both magnetic resonance imaging and ultrasound are non-invasive tests with equivalent accuracy in diagnosing adenomyosis (area under curve 0.91 and 0.88, respectively). Most studies on treatments have been uncontrolled and outcomes are usually reported in the form of case series. Hence, the true impact of various treatments on fertility is not known. There are variable reports of the impact of adenomyosis on the success of IVF. Increased incidence of preterm labour and premature rupture of membranes has been reported in women with adenomyosis.
CONCLUSIONS: Further studies are needed to determine the natural history of adenomyosis and implications for fertility and reproductive outcomes, with and without treatment. Currently, there is no evidence that we should find and treat adenomyosis in patients who wish to conceive.

Key words: adenomyosis / subfertility / MRI / ultrasound / fertility outcomes

Introduction

Uterine adenomyosis is a pathological condition characterized by the presence of endometrial glands and stroma within the myometrium. It is generally agreed that adenomyosis occurs when the normal boundary between the endometrial basal layer and the myometrium is disrupted. As a consequence, endometrial glands are able to invade the myometrium, giving rise to ectopic intramyometrial glands that cause hypertrophy and hyperplasia of adjacent myometrium (Vercellini et al., 2006).

The definite diagnosis of adenomyosis is based on a histological examination, usually on a hysterectomy specimen. With a quoted prevalence ranging from 8 to 27%, it was initially thought to be a condition of parous women, with the final diagnosis made after hysterectomy. Thus, an association between adenomyosis and subfertility has not been fully established. Some believe that adenomyosis is not common in subfertile women, while others think that adenomyosis plays a critical role in subfertility (Kissler et al., 2008).

Uterine adenomyosis is usually diagnosed in the fourth and fifth decade of life. Since more women are tending to delay their first pregnancy till their late thirties or early forties, adenomyosis has become more relevant in the context of subfertility. Moreover, with better imaging techniques, it is being increasingly diagnosed in women otherwise labelled as having ‘unexplained infertility’. As hysterectomy is not an option in women wishing to preserve their fertility, a number of conservative interventions have been advocated, with variable reports of their impact on spontaneous, as well as treatment-related, conceptions. This presents a dilemma for clinicians managing such patients.

The aims of this systematic review were to determine (i) the prevalence of adenomyosis in infertile women, (ii) the accuracy of diagnostic tests for adenomyosis, (iii) the efficacy of fertility-preserving treatments in subfertile women and (iv) the reproductive and perinatal outcomes in women with adenomyosis.

Methods

Search strategy

Systematic searches of MEDLINE, EMBASE, CDSR, DARE and PUBMED (1948–2011) were performed independently by two reviewers (S.G. and F.F.) using the key words ‘adenomyosis, adenomyoma, infertility, treatment, prevalence, diagnosis, IVF, assisted reproduction, pregnancy and obstetric outcomes’. Leading fertility journals (Human Reproduction Update; Human Reproduction; Fertility & Sterility; Human Fertility; Reproductive Biomedicine Online; Journal of Assisted Reproduction and Genetics) along with appropriate cross references were hand-searched for relevant articles. The topics covered were (i) the prevalence of adenomyosis in a subfertile population, (ii) accuracy of diagnostic tests of adenomyosis, (iii) fertility sparing treatment options of adenomyosis and (iv) reproductive and obstetric/perinatal outcome in women with adenomyosis. All studies were included according to predetermined and agreed inclusion criteria, the details of which are presented in the following section. There was no language restriction. All animal studies were excluded.

Inclusion and exclusion criteria

Prevalence

Articles that explored the prevalence of adenomyosis in subfertile women were included. Where the prevalence of endometriosis and adenomyosis were both reported, only those articles where it was possible to separate the two conditions were included.

Diagnosis

All studies exploring the accuracy of various modalities for the diagnoses of adenomyosis were included if 2 × 2 tables could be generated. Where 2 × 2 tables could not be generated, we wrote to authors to obtain the missing data. If two studies were reported from same group during an overlapping time period, in order to avoid double counting, only the largest or later study was included.

Treatment

All studies exploring fertility-preserving treatments for adenomyosis in women of reproductive age were included if they reported pregnancy as an outcome measure. Studies on hysterectomy, insertion of an intrauterine device and endometrial ablation were excluded. Randomized controlled trials and observational studies were included. Where the treatment of both adenomyosis and endometriosis were evaluated, studies were only included if it was possible to obtain outcome data for adenomyosis only. Only studies where outcome measures included symptomatic or radiological improvement were excluded.

Impact on conception and obstetric outcomes

Studies were included only if they reported treatment-independent or treatment-related reproductive and obstetric/perinatal outcomes in women with adenomyosis, separate from endometriosis.

Data extraction and analysis

Data were extracted independently by two reviewers (S.G. and A.M.) according to a predefined criteria. Any discrepancies were resolved after discussion with S.B. and A.M. Contact with primary authors was attempted wherever appropriate. Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidance was followed wherever applicable.

If pooling of data was not possible, a narrative approach was used to describe the studies. Meta disc (version 4.2) was used to determine the diagnostic accuracy. ROC (receiver operating characteristic) curves were plotted, and area under curve (AUC) was calculated where applicable.
Assessing study quality

Prevalence
There was no specific tool/scoring to assess the quality of prevalence studies, but care was taken to determine whether the following were specified: target population, inclusion criteria, sampling method, valid and repeatable disease definition and estimates of prevalence.

Diagnosis
QUADAS (quality assessment tool for diagnostic accuracy studies) was used to score the studies on the diagnostic tests. All 14 parameters for QUADAS were assessed (Whiting et al., 2003).

Treatment
Studies evaluating treatment were uncontrolled retrospective studies or case series; hence no specific tool was used to assess the quality.

Impact on conception and obstetric outcomes
The quality of these studies was evaluated according to the check list in the critical studies skills programme for case–control (http://www.sph.nhs.uk/sph-files/Case%20Control%2011%20Questions.pdf) and cohort (http://www.sph.nhs.uk/sph-files/cohort%2012%20questions.pdf) studies.

Results

Prevalence
Identification of studies
A total of 15 studies were identified, of which 11 articles were excluded (four were excluded at the abstract stage, as they did not fulfill pre-determined inclusion criteria and five were reviews, comments and letters). Of the four full-text articles that were evaluated further (de Souza et al., 1995; Kunz et al., 2005, 2007; Kessler et al., 2008), Kunz et al. (2007) was excluded as there was overlap of data with Kunz et al. (2005). Hence, three studies were finally included (Table I).

Results
The gold standard for diagnosis of adenomyosis was magnetic resonance imaging (MRI) in all three included studies. Only one study included a population from infertility clinic only (Kunz et al., 2005). In this study, adenomyosis was diagnosed by MRI in 79% of those with endometriosis when compared with 28% of those without. This study was based on a total of 227 women; however, it is not clear how many women from the clinic were not recruited. In another series that included 26 patients with infertility and menorrhagia or dysmenorrhoea, adenomyosis was found in 14 (53.8%) women (de Souza et al., 1995). Again, it is not reported as to how many were attending infertility clinic without menorrhagia had adenomyosis. The third study (Kessler et al., 2008) included women with dysmenorrhoea only, of which 43% were infertile but it does not give a separate prevalence of adenomyosis in this population. Hence, the exact prevalence from an infertility clinic population cannot be determined.

Although MRI was used as the gold standard in all three studies, the criteria used for confirmation of the diagnosis varied slightly, implying that there are no internationally agreed definitions. Kunz et al. (2005) used expansion of anterior and posterior junctional zone (without mentioning any specific thickness), whereas Kessler et al. (2008) used a junctional zone thickness of >9 mm. All three studies included women of reproductive age.

Diagnosis
Of 351 studies identified initially, 44 full-text papers, containing 48 studies of different diagnostic techniques, were evaluated further (Fig. 1). Seven different modalities of diagnosis have been studied [computed tomography (CT)-1; Biopsy-9; Sonohysteroscopy-1; Doppler-1; Ultrasound-23; MRI-9; Unclassified-4]. Of these, only 23 studies could be included for further analysis, as shown in Fig. 1. Details of included articles are summarized in Tables II, III and IV. A list of excluded studies along with reasons for their exclusion is provided in Supplementary data, Table S1.

Biopsy
Three of the included studies evaluated targeted biopsy prior to hysterectomy for the diagnosis of adenomyosis (Table II). All were prospective studies and included histopathology results on uterine specimens from women undergoing hysterectomy for benign conditions as reference standards. However, the method of taking a biopsy was different in each (laparoscopic guided, Brosens et al., 1995; laparoscopic and ultrasound guided (Jeng et al., 2007) and on hysterectomy specimens (Vercellini et al., 1998)). The actual number of biopsies per patient varied from 1 to 10 (1 by Vercellini et al., 1998 and 10 by Brosens et al., 1995) although all used a 14-gauge needle. The pooled data for targeted biopsy show that sensitivity, specificity, positive likelihood ratio and negative likelihood ratio with 95% confidence intervals (CIs) were 0.77 (0.70-0.84); 0.97 (0.91-0.93); 11.86 (4.34–32.44), 0.28 (0.11–0.71), respectively, with an area under the ROC curve of 0.98. Although the positive likelihood ratio was high (11.86), the 95% CIs were very wide (4.34–32.44).

Methodological quality of included studies. All three studies had high QUADAS scores (10, 12 and 13 of 14 items). Indeterminate results were not reported by any of them. Blinding of the reference standard to the index test and vice versa was present in two of the three studies (Vercellini et al., 1998; Jeng et al., 2007).

Ultrasound
Identification of studies. There were 14 studies of ultrasound assessments where 2 × 2 tables could be generated (Fig. 1). We also identified some overlapping studies. Data were taken from a later study (Bazot et al., 2002); hence the study by Bazot et al. (2001) was excluded for ultrasound (USG) tests. Data were included only from transvaginal USGs (TV USG).

All of the studies used histopathology of hysterectomy specimens as the gold standard except the study by Ascher et al. (1994), which included some cases where myometrial biopsy was used as the gold standard instead of hysterectomy, but these could not be identified separately. Brosens et al. (1995) had a group with MRI as the gold standard; however pooling of data was not feasible because no other study evaluating USGs had used MRI as the gold standard.

Definition of adenomyosis on USG. USG parameters used define adenomyosis included: (i) heterogeneous myometrial area, (ii) globular asymmetric uterus, (iii) irregular cystic spaces, (iv) myometrial linear...
striations, (v) poor definition of endometrial myometrial junction, (vi) myometrial anterior posterior asymmetry and (vii) thickening of anterior and posterior myometrial wall and increased or decreased echogenecity. Some studies have used only one of these parameters (Vercellini et al., 1998), while others required the presence of all to diagnose adenomyosis (Sun et al., 2010).

Reference standard—definition of reference standard. Histopathology of a hysterectomy specimen was the most common reference standard. However, the criteria used for confirmation of adenomyosis in some studies was distance between the lower border of endometrium and the affected myometrial area of more than one half of a low power field, whereas others thought that adenomyosis could only

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**Table I** Studies exploring the prevalence of adenomyosis.

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Type of study</th>
<th>Inclusion criteria</th>
<th>Diagnosis confirmed by</th>
<th>Definition of adenomyosis on gold standard</th>
<th>Denominator</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kissler et al. (2008)</td>
<td>70 women</td>
<td>Prospective</td>
<td>Patients presenting with the complaint of severe dysmenorrhoea were divided into two groups: those with &lt;10 years of symptoms (mean age: 30.07 years) and those with &gt;10 years of symptoms (mean age: 33.31 years)</td>
<td>MRI</td>
<td>Maximal JZ thickness 9 mm or greater</td>
<td>Women with severe dysmenorrhoea Thirty patients with infertility but prevalence in those 30 patients is not known. Written to authors but no response</td>
<td>Dysmenorrhoea 1–10 years: 52.5%</td>
</tr>
<tr>
<td>de Souza et al. (1995)</td>
<td>26 women</td>
<td>Prospective</td>
<td>Age: 26–41 years (mean: 34.3 years); 18 months of infertility All had laparoscopy performed as routine work up</td>
<td>MRI</td>
<td>Focal adenomyosis: localized ill-defined mixed signal intensity mass (adenomyoma) within the myometrium; Diffuse adenomyosis: diffuse or irregular thickening of the junctional zone often with underlying high signal foci</td>
<td>Women with dysmenorrhoea and menorrhagia, and from infertility clinic</td>
<td>14/26 (53.8%)</td>
</tr>
<tr>
<td>Kunz et al. (2005)</td>
<td>227 women</td>
<td>Prospective</td>
<td>Cases—in fertile women with endometriosis, diagnosed at laparoscopy. Control group of infertile women with no endometriosis (mean age: 32.65 years, range: 17–46 years)</td>
<td>MRI</td>
<td>Diffuse adenomyosis: expansion of the posterior junctional zone (PJZ) and/or anterior junctional zone (AJZ) along the whole length of the uterine cavity Focal adenomyosis: expansions of the PJZ and/or AJZ that is of variable shape and size and that did not extend over the whole length of the uterine cavity. JZ thickness of &gt;10 mm or lesions presenting as hypointense protrusions with variable sizes and locations from the junctional zone into the outer myometrial wall</td>
<td>Women from infertility clinic with and without endometriosis. (160 women with endometriosis and 67 without endometriosis)</td>
<td>79% with endometriosis 28% without endometriosis</td>
</tr>
</tbody>
</table>
be diagnosed when endometrial glands and stroma lay deeper than 2.5 mm below the endometrial surface on a low power field.

Population studied. Most studies included women between 29 and 72 years who were undergoing hysterectomy for benign conditions. Most studies included women with menstrual symptoms suggestive of adenomyosis.

Methodological quality of included studies. Of the 14 included studies, 11 scored at least 10 on the QUADAS scoring. All were prospective except for Siedler et al. (1987) and Sun et al. (2010). Indeterminate tests were not mentioned by any except Vercellini et al. (1998). Withdrawals from study, and time intervals between reference and index test were not clearly reported by most. The exact definition of reference standard was not given by four studies (Table III).

Results of the pooled data. The pooled sensitivity, specificity, positive likelihood ratio and negative likelihood ratio (95% CI) of TV USG to diagnose adenomyosis were 0.79 (0.75–0.83), 0.85 (0.82–0.87), 5.43 (3.35–8.78) and 0.27 (0.20–0.37), respectively. The AUC was 0.88.

A sensitivity analysis, after removing poor quality studies (QUADAS <10), did not alter the results.

Magnetic resonance imaging. There were a total of six studies that evaluated the role of MRI in the diagnosis of adenomyosis and yielded data to inform $2 \times 2$ tables. Uterine histopathology based on a hysterectomy specimen was used as a reference standard in all of them. Ascher et al. (1994) included some cases where myometrial biopsy was used as the gold standard but data pertaining to these could not be disaggregated from the remainder. All the included studies targeted a similar population of women undergoing hysterectomy for a benign condition.

Definition of adenomyosis on MRI. Criteria for the definition of adenomyosis on MRI were: (i) a myometrial mass with indistinct margins of primarily low intensity, (ii) diffuse or local widening of junctional zones on T2 weighted images, (iii) junctional zone thickness
> 15 mm, (iv) subjective thickening of junctional zone, localized or diffuse, (v) ill-defined low intensity lesion, (vi) junctional zone wider than 12 mm, (vii) uterine enlargement or (viii) small hypointense myometrial spots.

A variable combination of the earlier-mentioned criteria was used by the included studies; some used only one, whereas others used more than one.

Methodological quality of the included studies. Four studies scored high on QUADAS criteria. An indeterminate test was not reported by any of the studies except Ascher et al. (1994). Two studies (Togashi et al., 1989; Moghadam et al., 2006) included some cases with reference standards as histopathology examination of myomectomy and myometrial biopsy. Blinding of reference standard to index test was unclear in two studies (Togashi et al., 1989; Moghadam et al., 2006).

Results of the pooled data. The pooled sensitivity, specificity, positive likelihood ratios and negative likelihood ratios (with 95% CI) for the diagnostic accuracy of MRI in this context were 0.74 (0.67–0.81), 0.91 (0.88–0.93), 6.20 (3.70–10.41) and 0.25(0.12–0.55), respectively. The AUC was 0.91. A sensitivity analysis after removing two low score studies did not alter the results.

Treatment

Of 410 titles identified in initial searches on adenomyosis and treatment, 43 studies merited further evaluation of the full-text versions (after excluding studies on hysterectomy, intrauterine contraceptive devices, endometrial ablation, reviews and duplicates). There were 21 articles further excluded as they did not report pregnancy as an outcome measure, and two studies reporting pregnancy outcomes were excluded (Kim et al. (2005) for overlapping data with their 2004 article, and

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Reference standard</th>
<th>Definition of adenomyosis by reference standard</th>
<th>Population</th>
<th>Method of biopsy</th>
<th>QUADAS score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brosens et al. (1995)</td>
<td>Prospective non-randomized</td>
<td>Histopathology of the hysterectomy specimen</td>
<td>A needle biopsy was considered positive if glandular tissue was sandwiched between strips of myometrium</td>
<td>40 women who were about to undergo hysterectomy</td>
<td>Eight needle biopsies were taken perpendicular to the serosal surface using a Pro-Mag 2.2 biopsy system with an automatic cutting needle (14 gauge). Four biopsies were taken from anterior half of the uterus and four from posterior half</td>
<td>10</td>
</tr>
<tr>
<td>Jeng et al. (2007)</td>
<td>Prospective non-randomized</td>
<td>Histopathology of the hysterectomy specimen</td>
<td>Not defined</td>
<td>100 women with clinical signs and symptoms (uterine enlargement, severe dysmenorrhoea and menorrhagia) strongly suggestive of adenomyosis</td>
<td>10 myometrial biopsy were taken per patient with a 14-gauge Tru-Cut needle through abdominal wall from locations suspected to have adenomyosis as determined by transvaginal ultrasound</td>
<td>12</td>
</tr>
<tr>
<td>Vercellini et al. (1998)</td>
<td>Prospective non-randomized</td>
<td>Histopathology of the hysterectomy specimen</td>
<td>Not defined</td>
<td>102 consecutive premenopausal women with a uterus measuring &lt;12 week pregnancy undergoing hysterectomy for menorrhagia and/or worsening dysmenorrhoea</td>
<td>A single full thickness biopsy was taken along the median line in the upper third of posterior uterine wall, using 14-gauge Tru-Cut needle</td>
<td>13</td>
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</table>

Adenomyosis and subfertility
<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Reference standard</th>
<th>Definition of adenomyosis on ultrasound</th>
<th>Number of women</th>
<th>Inclusion criteria</th>
<th>QUADAS Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vercellini et al. (1998)</td>
<td>Prospective non-randomized</td>
<td>Histopathology of hysterectomy specimen</td>
<td>The presence of indistinctly demarcated heterogeneous myometrial areas with distorted echotextures</td>
<td>102 consecutive women</td>
<td>Mean age: 45 ± 6 years. Premenopausal women with a uterus measuring &gt; 12 week pregnancy undergoing hysterectomy for menorrhagia and/or worsening dysmenorrhea. Exclusion criteria: women with grossly distorted uterus with multiple leiomyoma or with known endo cavity or endometrial abnormalities who received hormonal therapy.</td>
<td>14</td>
</tr>
<tr>
<td>Kocak et al. (1998)</td>
<td>Prospective</td>
<td>Histopathology of hysterectomy specimen</td>
<td>Heterogeneous myometrial areas which are not encapsulated and contain an echoic lacuna measuring 1–3 mm in diameter; and an area characterized by irregular cystic spaces measuring 5–7 mm in diameter and disrupting the normal fine speckled echo pattern of the uterus</td>
<td>40 parous women</td>
<td>Mean age: 48.7 years (38–60 years). Women suspected of having endometriosis because of menorrhagia, pelvic pain and enlarged uterus.</td>
<td>8</td>
</tr>
<tr>
<td>Bazot et al. (2002)</td>
<td>Prospective (January 1996–April 1998)</td>
<td>Histopathology of hysterectomy specimen</td>
<td>A globular and asymmetric uterus, a poorly defined focus of abnormal myometrial echotexture, distorted and heterogeneous myometrial echotexture, myometrial linear striations (radiate pattern of thin acoustic shadowing) and myometrial cysts (1–7 mm in diameter)</td>
<td>129 consecutive women who underwent hysterectomy</td>
<td>The presence of ectopic endometrial tissue within the myometrium, located 2.5 mm beyond the endometrial myometrial junction.</td>
<td>12</td>
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<tr>
<th>Study</th>
<th>Type</th>
<th>Reference standard</th>
<th>Definition of adenomyosis on ultrasound</th>
<th>Number of women</th>
<th>Inclusion criteria</th>
<th>QUADAS Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kepkep et al. (2007)</td>
<td>Prospective (January 2003–April 2004)</td>
<td>Histopathology of hysterectomy specimen</td>
<td>Heterogeneous myometrial echotexture, globular appearing uterus, asymmetrical thickening of antero-posterior wall of myometrium, subendometrial myometrial cyst, subendometrial echogenic linear striations or poor definition of endometrial, myometrial junction</td>
<td>70 consecutive women selected for hysterectomy mean age: 49.03 ± 5.58 years (37–63 years)</td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>Reinhold et al. (1996)</td>
<td>Prospective study</td>
<td>Histopathologic examination</td>
<td>Poorly defined area of abnormal echotexture noted within the myometrium. Abnormal myometrium was defined as an area demonstrating heterogeneity, decreased or increased echogenicity and or the presence of myometrial cyst</td>
<td>119 consecutive patients undergoing hysterectomy meeting inclusion criteria</td>
<td></td>
<td>13</td>
</tr>
<tr>
<td>Atzori et al. (1996)</td>
<td>Prospective study</td>
<td>Histopathology of hysterectomy specimen</td>
<td>Heterogeneous myometrial areas that are not encapsulated and contain anechoic lacunae measuring 1–3 mm in diameter and an area characterized by irregular cystic spaces measuring 5–7 mm in diameter and disrupting the normal fine speckled echopattern of the uterus</td>
<td>170 women with mean age of 45.8 years (37–62 years) prior to hysterectomy for benign uterine pathology</td>
<td></td>
<td>10</td>
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<td></td>
<td></td>
<td></td>
<td>Diagnosed only if the distance between lower border of the endometrium and the adenomyosis exceeded ~2.5 mm</td>
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<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Reference standard</th>
<th>Definition of adenomyosis on ultrasound</th>
<th>Number of women and Inclusion criteria</th>
<th>QUADAS Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sun et al.</td>
<td>Retrospective study (blinded)</td>
<td>Histopathology of hysterectomy specimen</td>
<td>Globular uterine configuration, poor definition of endometrial-myometrial interface, sub-endometrial echogenic linear striations, myometrial anterior posterior asymmetry, myometrial cysts and heterogeneous myometrial texture</td>
<td>213 consecutive patients scheduled for hysterectomy. Mean age: 27–73 years (mean: 44.72 =/− 6.83 years)</td>
<td>11</td>
</tr>
<tr>
<td>Brosens et al.</td>
<td>Prospective study (November 1992–July 1993)</td>
<td>Histopathology of hysterectomy specimen or MRI</td>
<td>Adenomyosis suspected if there was a degree of uterine enlargement, uterine asymmetry not due to fibroids and heterogeneity of myometrial echoes</td>
<td>56 women with menorrhagia and dysmenorrhoea. Distance between lower the lower border of endometrium and the affected areas was over one half of low power field</td>
<td>7</td>
</tr>
<tr>
<td>Fedele et al.</td>
<td>Prospective (October 1988–October 1990)</td>
<td>Histopathology of hysterectomy specimen</td>
<td>The presence of one or more heterogeneous myometrial area not encapsulated and within round an echoic area of 1–3 cm in diameter</td>
<td>43 women with age of 46 ± 5 years. Women with recurrent menorrhagia, enlarged uterus, without evidence of leiomyomas at pelvic examination and USG and no endometrial disease at Vabra curettage. Exclusion criteria: hormonal therapy within last 2 months</td>
<td>10</td>
</tr>
<tr>
<td>Ascher et al.</td>
<td>Prospective blinded</td>
<td>Either myometrial biopsy or histology of hysterectomy specimens</td>
<td>Thickening and asymmetry of anterior and posterior myometrial walls, increased echotexture of myometrium, heterogeneous, indistinctly margined areas in the myometrium</td>
<td>20 women aged 25–63 years (mean age: 36.6 years). Women in whom adenomyosis was suspected on the basis of unexplained pelvic pain, menorrhagia and lack of evidence of leiomyoma on USG</td>
<td>12</td>
</tr>
<tr>
<td>Dueholm et al.</td>
<td>Prospective double-blinded study</td>
<td>Histopathological examination</td>
<td>The presence of focal areas with not well-defined borders or abnormal echotexture was taken as diagnosis of adenomyosis, in addition, the presence of heterogeneity, increased or decreased area of echogenicity, or presence of myometrial cyst</td>
<td>106 consecutive women who underwent hysterectomy for benign reasons</td>
<td>12</td>
</tr>
</tbody>
</table>
Lin et al. (1999) had overlapping data with their 2000 article. No randomized controlled trials were found. Two studies were retrospective comparative studies (Morita et al., 2004; Takeuchi et al., 2006) evaluating different interventions; hence pooling of data was not deemed appropriate. The remainders were all case series (14 studies) or case reports (6 studies). Table V gives details of all included studies evaluating fertility-preserving surgery for women with adenomyosis with pregnancy as an outcome measure. We have refrained from doing any meta-analysis due to the study designs (case series and case reports), even where the same intervention was evaluated.

The results revealed a wide variety of treatments for the conservative management of adenomyosis in subfertile patients. They include

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**Table III** Continued

<table>
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<tr>
<th>Study</th>
<th>Type</th>
<th>Reference standard</th>
<th>Definition of adenomyosis on ultrasound</th>
<th>Number of women</th>
<th>Inclusion criteria</th>
<th>QUADAS Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siedler et al. (1987)</td>
<td>Retrospective review</td>
<td>Histopathologic examination of hysterectomy specimen</td>
<td>The presence of endometrial glands or stroma deep in the endomyometrial junction and the diagnostic criteria of adenomyosis was satisfied when it exceeded one medium power (∇×100) field</td>
<td>Mean age: 44.7 ± 5.2 years</td>
<td>Only 70 patients were included in the analysis as 36 patients had indefinite diagnosis (33 on HPE and 3 on USG)</td>
<td>8</td>
</tr>
<tr>
<td>Botsis et al. (1997)</td>
<td>Prospective study (1993–1994)</td>
<td>Histopathologic diagnosis of adenomyosis</td>
<td>Diffusely enlarged uterus but the myometrial texture, contour and central echoes were each normal</td>
<td>80 women (29–72 years) who had a pre operative pelvic ultrasound examination; subsequent hysterectomy and a histologic diagnosis of leiomyoma and/or adenomyosis</td>
<td>Sonographic criteria for definition of adenomyosis were heterogeneous myometrial areas that were not encapsulated and that contained anechoic lacunae measuring 1–3 mm in diameter and an area characterized by irregular cystic spaces measuring 1–7 mm in diameter (honey-cobomb pattern) and disrupting the normal fine speckled echo pattern of the uterus. The sonographic diagnosis of adenomyosis was made when at least three parameters were positive</td>
<td>11</td>
</tr>
<tr>
<td>Huang et al. (1995)</td>
<td>Prospective study (January–November 1993)</td>
<td>Histopathologic examination of hysterectomy specimen</td>
<td>Adenomyosis was diagnosed when there was an unhomogeneous circumscribed area in the myometrium, with an indistinct margin, containing hypoechoic spaces &gt;5 mm</td>
<td>140 women who underwent hysterectomy for benign indication</td>
<td>Endometrial glands and stroma found within the myometrium more than one high power microscopic field below the basal endometrium</td>
<td>11</td>
</tr>
</tbody>
</table>

USG, ultrasound.
### Table IV  Studies regarding diagnosis: MRI.

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Reference standard</th>
<th>Definition of adenomyosis on MRI</th>
<th>Number of women inclusion criteria</th>
<th>QUADAS score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascher et al. (1994)</td>
<td>Prospective</td>
<td>Either myometrial biopsy or histology of hysterectomy specimens</td>
<td>MRI criteria for diagnosis was (i) a myometrial mass with indistinct margins of primarily low intensity with all sequences or (ii) diffuse or focal widening (&gt;0.5 cm) of the junctional zone on T2 weighed images</td>
<td>20 women aged 25—63 years (mean age: 36.6 years) women in whom adenomyosis was suspected on the basis of unexplained pelvic pain, menorrhagia and lack of evidence of leiomyoma on USG</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Results of index test interpreted blindly to reference standard</td>
<td>Histological diagnosis is made when a specimen contained endometrial glands and stroma lying deeper than 2.5 mm below the endometrial surface</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dueholm et al. (2001)</td>
<td>Prospective</td>
<td>Histopathological examination</td>
<td>Diffuse adenomyosis is thought to be present when JZ max &gt;15 mm. For a thickness of 12–15 mm adenomyosis was thought to be present when one of the criteria was met: non-uniform thickened JZ or focal non well demarcated high or low intensity areas of myometrium</td>
<td>106 consecutive women who underwent hysterectomy for benign reasons</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Results of index test interpreted blindly to reference standard</td>
<td>The presence of endometrial glands or stroma deep in the endo-myometrial junction and the diagnostic criteria of adenomyosis was satisfied when it exceeded one medium power (× 100) field</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reinhold et al. (1996)</td>
<td>Prospective</td>
<td>Histopathologic examination diagnosed by the presence of endometrial glands and/or stroma greater than one high power field deep to endometrial myometrial junction</td>
<td>The diagnosis of adenomyosis was made on MRI when there was a subjective impression of localized or diffuse thickening of the uterine JZ (with or without the presence of small foci of increased signal intensity myometrial mass with ill-defined borders</td>
<td>64 premenopausal and 55 post-menopausal women</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Results of index test interpreted blindly to reference standard</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Continued...
intrauterine insertion of danazol-loaded devices, GnRH agonist therapy, combination therapy of conservative surgery with a GnRH agonist, conservative surgery alone, high intensity focused USG, uterine artery embolization, laparoscopic partial resection with uterine artery occlusion and myometrectomy. The outcome measures for each type of treatment are discussed followingly.

**Insertion of danazol-loaded devices**

We identified two case series reports that evaluated the use of a danazol-loaded intrauterine device (Igarashi et al., 2000) or a vaginal ring (Igarashi, 1990) in patients with adenomyosis requiring fertility preservation. The combined pregnancy rate after insertion and removal of these devices was 41% (16 of 39).

**GnRH agonist therapy**

There were two case series and a case report reporting successful use of GnRH agonist alone in the conservative treatment of adenomyosis (Nelson and Corson, 1993; Huang et al., 1999; Lin et al., 2000). Long-term use of GnRHa resulted in spontaneous pregnancy in all three studies (6 of 7) within 24 months of cessation (Table V).

**Combination of conservative surgery with GnRH agonist/danazol**

Our search identified eight studies evaluating conservative surgery with or without GnRH agonist. Four of these were case series, and four were case reports. The pooled live birth rate after this mode of treatment was 88.2% (15 of 17) (Table V). Six of these studies used GnRHa post-operatively and the other two used danazol.

---

### Table IV

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Reference standard</th>
<th>Definition of adenomyosis on MRI</th>
<th>Number of women inclusion criteria</th>
<th>QUADAS score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Togashi et al. (1989)</td>
<td>Prospective study</td>
<td>Histopathological examination of hysterectomy, myomectomy or biopsy specimens</td>
<td>Adenomyosis was confirmed when there was a low signal intensity lesion that was ill-defined</td>
<td>93 women (mean age: 41 years; age range: 21–62 years) with enlarged uterus that was clinically suspect of leiomyoma or adenomyosis were included in the prospective study Exclusion criteria: suspicion of endometrial or cervical cancer</td>
<td>8</td>
</tr>
<tr>
<td>Moghadam et al. (2006)</td>
<td>Retrospective review</td>
<td>Histopathological examination of hysterectomy and myomectomy specimens</td>
<td>Adenomyosis was described as focal or diffuse widening of junctional zone above 12 mm, uterine enlargement, or both, with focal or diffuse low intensity myometrial area in T2 weighted images small hypointense myometrial spots were indicative of adenomyosis</td>
<td>153 women (21–69 years) mean age: 41 years</td>
<td>9</td>
</tr>
<tr>
<td>Bazot et al. (2001)</td>
<td>Prospective study</td>
<td>Histopathology of hysterectomy specimen</td>
<td>Adenomyosis was defined by (i) a large, regular asymmetric uterus without leiomyomas, (ii) JZof at least 12 mm and/or an ill-defined, low signal intensity myometrial area distinguished from well circumscribed mass related to myoma, (iii) ratio &gt;40% and (iv) punctuate high intensity myometrial foci</td>
<td>50 had hysterectomy and 103 had myomectomy Women who were admitted to undergo hysterectomy and underwent MRI as well. 153 women were identified</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Results of index test interpreted blindly to reference standard</td>
<td>The presence of ectopic endometrial tissue within the myometrium, located 2.5 mm beyond the endometrial myometrial junction</td>
<td>120 consecutive women referred for hysterectomy Of 167 eligible women 47 were excluded due to unavailability of index/reference test. Mean age was 51 years</td>
<td></td>
</tr>
</tbody>
</table>

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danazol-loaded devices, GnRH agonist therapy, combination therapy of conservative surgery with a GnRH agonist, conservative surgery alone, high intensity focused USG, uterine artery embolization, laparoscopic partial resection with uterine artery occlusion and myometrectomy. The outcome measures for each type of treatment are discussed followingly.

**Insertion of danazol-loaded devices**

We identified two case series reports that evaluated the use of a danazol-loaded intrauterine device (Igarashi et al., 2000) or a vaginal ring (Igarashi, 1990) in patients with adenomyosis requiring fertility preservation. The combined pregnancy rate after insertion and removal of these devices was 41% (16 of 39).
Table V  Studies exploring conservative treatments and reporting pregnancy as an outcome.

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study</th>
<th>Intervention</th>
<th>No. of patients</th>
<th>Age range</th>
<th>Mode of diagnosis</th>
<th>Follow-up</th>
<th>Type of adenomyosis</th>
<th>Time to pregnancy</th>
<th>Outcome measure</th>
<th>Number of women who got pregnant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrospective studies</td>
<td></td>
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<tr>
<td>Wang et al. (2009)</td>
<td>Retrospective</td>
<td>Conservative surgery ± agonist versus GnRH agonist alone</td>
<td>65</td>
<td>30–36</td>
<td>TVS</td>
<td>3 years</td>
<td>nm</td>
<td>12–36 m</td>
<td>Pregnancy, Live birth</td>
<td>32.4 versus 8%</td>
</tr>
<tr>
<td>Fujishita et al. (2004)</td>
<td>Retrospective</td>
<td>Old classical reduction surgery versus modified H incision technique</td>
<td>7</td>
<td>27–40</td>
<td>USG/MRI</td>
<td>23–69 months</td>
<td>Focal and diffuse</td>
<td>4, 6 months</td>
<td>Pregnancy</td>
<td>0 versus 50%</td>
</tr>
<tr>
<td>Case series and case reports</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Igarashi et al. (2000)</td>
<td>Case series</td>
<td>Danazol-loaded intrauterine device</td>
<td>4</td>
<td>nm</td>
<td>MRI</td>
<td>nm</td>
<td>nm</td>
<td>nm</td>
<td>Pregnancy</td>
<td>3/4</td>
</tr>
<tr>
<td>Igarashi (1990)</td>
<td>Case series</td>
<td>Danazol-loaded vaginal ring</td>
<td>35</td>
<td>nm</td>
<td>nm</td>
<td>nm</td>
<td>nm</td>
<td>nm</td>
<td>Pregnancy</td>
<td>13/35</td>
</tr>
<tr>
<td>Huang et al. (1999)</td>
<td>Case series</td>
<td>Nafrelin nasal spray 3 months</td>
<td>2</td>
<td>nm</td>
<td>nm</td>
<td>6 months</td>
<td>nm</td>
<td>6 m</td>
<td>Pregnancy</td>
<td>2/2</td>
</tr>
<tr>
<td>Nelson and Corson (1993)</td>
<td>Case report</td>
<td>GnRHa (long-term) Leuprolide acetate 0.5 mg s for 6 months given three times over 2 years</td>
<td>1</td>
<td>19</td>
<td>USG</td>
<td>nm</td>
<td>Diffuse</td>
<td>nm</td>
<td>Pregnancy</td>
<td>1/1</td>
</tr>
<tr>
<td>Lin et al. (2000)</td>
<td>Case series</td>
<td>GnRHa for 6 months</td>
<td>4</td>
<td>nm</td>
<td>nm</td>
<td>nm</td>
<td>nm</td>
<td>nm</td>
<td>Pregnancy</td>
<td>3/4</td>
</tr>
<tr>
<td>Wang et al. (2006)</td>
<td>Case series</td>
<td>Endometriotic cystectomy, adenomyomectomy + post op. danazol 3 m (1)</td>
<td>2</td>
<td>27, 38</td>
<td>USG</td>
<td>30 months</td>
<td>Focal</td>
<td>21, 30 months</td>
<td>Live birth</td>
<td>2/2</td>
</tr>
<tr>
<td>Jinfang et al. (2000)</td>
<td>Case series</td>
<td>Adhesiolysis, endocoagulation of endometriotic spots, adenomyomectomy (2) cases + 6 m post op. triptorelin (3)</td>
<td>4</td>
<td>23–41</td>
<td>TVS</td>
<td>12 months</td>
<td>2 Focal (2)</td>
<td>2–4 menstrual periods</td>
<td>Live birth</td>
<td>3/4</td>
</tr>
<tr>
<td>Wang et al. (2000)</td>
<td>Case series</td>
<td>Adenomyomectomy with microsurgical technique + 2–6 m post op. goserelin acetate</td>
<td>3</td>
<td>32–37</td>
<td>TVS</td>
<td>12 months</td>
<td>Diffuse</td>
<td>3, 8, 12 months</td>
<td>Live birth</td>
<td>3/3</td>
</tr>
<tr>
<td>Author(s)</td>
<td>Type</td>
<td>Intervention</td>
<td>Duration</td>
<td>Tests</td>
<td>Outcome</td>
<td>Remarks</td>
<td></td>
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</tr>
<tr>
<td>Lin et al. (1999)</td>
<td>Case series</td>
<td>6 months GnRHa before laparoscopic surgery in one case and post op. in three cases</td>
<td>4</td>
<td>nm</td>
<td>Laparoscopy 6 months</td>
<td>Pregnancy 3/4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Nafrelin 6 months                                                                 | 1        | 37    | USG 10 weeks Focal | Pregnancy 1/1                              |
| Ozaki et al. (1999)       | Case report   | Pre op. Leuprolide 6 m + Resection of localized adenomyosis + post op.  
Danazol 12 w                        | 1        | 33    | MRI 12 months Focal | Not mentioned in abstract Live birth 1/1    |
| Huang et al. (1998)       | Case report   | Cytoreductive surgery + 6 m post op.  
GnRH agonist          | 1        | nm    | nm Diffuse | Not mentioned in abstract Live birth 1/1    |
| Silva et al. (1994)       | Case report   | Wedge biopsy at surgery + post op.  
Leuprolide 5 month      | 1        | 36    | Biopsy nm Focal | Live birth 1/1                              |
| Tadjerouni et al. (1995)  | Case series   | Sagittal hysterotomy; resection of the pathologic myometrium and suture   | 36       | 28–45 | nm nm nm nm | Live birth 15/36                            |
| Takeuchi et al. (2006)    | Case series   | Lap adenomyomectomy and hysteroplasty                                         | 14       | nm    | nm nm | Live birth 2/14                             |
| Strizhakov and Davydov (1995) | Case series | Myometrectomy  
Computer aided HSG + TVS | 8        | 18–34 | nm nm | <12 months Pregnancy 4/8                    |
| Kim et al. (2005)         | Case series   | Uterine artery embolization                                                  | 6        | 28–35 | MRI 35 months nm | Live birth 5/6 Three menstrual cycles later |
| Rabinovici et al. (2006)  | Case report   | High intensity focused ultrasound                                            | 1        | 36    | MRI 12 months Focal | Live birth 1/1                              |

nm, not mentioned.
There was a considerable heterogeneity in the type of GnRH agonist, the duration and timing of use as well as the mode of diagnosis of adenomyosis before treatment was offered. Only one retrospective study (Table V) comparing conservative surgery with GnRH agonist versus GnRH agonist alone (Wang et al., 2009) was identified. A total of 28 women with adenomyosis underwent conservative adenomyomectomy with or without post-operative Leuprolide every 4 weeks for 24 weeks, while 37 patients only received Leuprolide every 4 weeks for 24 weeks. The comparative live birth rates following conservative surgery versus GnRH agonist alone were 32.14 versus 8%, respectively. The odds of having a live birth with conservative surgery alone was 3.91 (95% CI, 1.06, 14.43) compared with that with GnRH agonist alone.

Conservative surgery alone
Three case series evaluated the effect of conservative surgery alone in women with adenomyosis. Two studies reported live birth rates (Tadjerouni et al., 1995; Takeuchi et al., 2006) and one reported pregnancy (Strizhakov and Davydov, 1995). The conservative surgical techniques described in all studies involve excision of the adenomyotic tissue or adenomyoma and hysteroplasty either laparoscopically or via laparotomy. An overall live birth rate of 36.2% (21 of 58) was achieved following the conservative surgery (Table V).

Comparison of two surgical techniques
A retrospective study (Fujisita et al., 2004) compared the classical method of adenomyomectomy with a new modified reduction surgery by means of a transverse H incision technique (Table V). The classical technique involved a uterine incision followed by step-wise resection of adenomyotic tissue and closure. The newer technique modified the incision to the shape of an H and this was followed by raising serosal flaps and excision of the adenomyomatous tissue. The new technique was associated with a 50% pregnancy rate, compared with no pregnancy with the older classical method. The odds of having a live birth with the old classical method compared with the newer technique was 0.14 (95% CI, 0.00 and 4.47). The time to pregnancy was 4 and 6 months, and one live birth and one ongoing pregnancy was reported up until the time of publication.

Uterine artery embolization
A single published study evaluated the effectiveness of uterine artery embolization in the management of adenomyosis and reported on pregnancy as an outcome (Kim et al., 2005). After a follow-up of 35 months (Table V), a live birth rate of 83.3% (five of six patients) was reported.

High intensity focused USG
High intensity focused USG is a recently developed therapeutic system that generates a high intensity acoustic beam that is precisely focused on a target area with MRI guidance to cause thermal coagulation. It has been previously used successfully in the treatment of uterine fibroids. The first successful live birth following this treatment in a patient with adenomyosis was reported in 2006 (Rabinovici et al., 2006) (Table V).

Impact of adenomyosis on fertility outcomes
Effect of adenomyosis on infertility
We were unable to identify any studies that aimed to explore the effect of adenomyosis on subsequent fertility by natural conception.

Effect of adenomyosis on assisted reproduction treatment
Four studies (Table VI) evaluated the effect of adenomyosis on the outcome of IVF treatment. One of them was a case series (Tremellen and Russell, 2011), two were case–control studies and one was retrospective cohort (Costello et al., 2011). Mijatovic et al. (2010) only included women with endometriosis (with or without adenomyosis) who were given prolonged down-regulation, whereas Costello et al. (2011) excluded women with endometriosis. Hence not all women with endometriosis were included. Martínez-Conejero et al. (2011) included only oocyte recipients. The results are conflicting with two studies suggesting no effect of adenomyosis (Mijatovic et al., 2010; Costello et al., 2011), and the other two showing increased rates of miscarriage or decreased implantation rates (Tremellen and Russell, 2011; Martínez-Conejero et al., 2011). However, of these latter studies, one is case series and other is on oocyte recipients. Pooling of data was not suitable because of the major differences in study design and populations in these studies. All studies except Martínez-Conejero et al. (2011) have given prolonged down-regulation to all women in the study.

Effect of adenomyosis on obstetric outcomes
One nested case–control study was identified as exploring the effect of adenomyosis on obstetric outcomes (Juang et al., 2007; Table VI). An increased risk of preterm delivery [odds ratio (OR) and 95% CI –1.84; 1.32–4.31] and preterm premature rupture of membrane (OR and 95% CI –1.98, 1.39–3.15) was found in women with adenomyosis when compared with those without adenomyosis. In addition, there have been 29 case reports (Aziz, 1986) on obstetric and/or surgical complications of adenomyosis (from years 1904 to 1984), such as uterine rupture or perforation, uterine atony leading to haemorrhage and ectopic pregnancies (including an ectopic pregnancy in an adenomyosis area). Another case report (Kim et al., 2006) reported rapid enlargement of adenomyosis in a pregnancy conceived after controlled ovarian hyperstimulation, leading to red degeneration and post-partum haemorrhage.

Discussion
There is little data on the epidemiology of adenomyosis associated with subfertility. There might be a higher prevalence of adenomyosis in a subfertile clinical population, especially in the presence of endometriosis and alongside symptoms such as dysmenorrhoea and/or menorrhagia. However, definite conclusions are not possible, with the current literature. Both MRI and USG are non-invasive tests with equivalent accuracy in diagnosing adenomyosis. However, there are no agreed criteria for diagnosing adenomyosis based on these tests. In fact, there is no international consensus on the histological criteria used to define adenomyosis in hysterectomy specimens, which is considered the gold standard. The method of performing biopsy for diagnosing adenomyosis also needs standardization.
Various conservative treatments have been described; however, most studies have been uncontrolled and outcomes are usually reported in the form of case series. Hence, the true impact of treatment on fertility is not known. Limited data suggest that the presence of adenomyosis in addition to endometriosis does not impair the outcomes in assisted reproduction, in women already treated with prolonged down-regulation. There is however an increased incidence of preterm labour and premature rupture of membranes in women with adenomyosis compared with those without (Juang et al., 2007).

This is an up-to-date systematic review of adenomyosis in subfertile populations. Although it is one review, it does consist of four distinct sections (prevalence; diagnosis; treatment; impact on IVF treatment and obstetric outcomes) and for each of them, there are separate inclusion and exclusion criteria and methodologies as well as different

Table VI: Studies exploring the effects of adenomyosis on fertility outcomes.

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Type of study</th>
<th>Population included</th>
<th>Confirmation of adenomyosis</th>
<th>Findings</th>
<th>Scoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tremellen and Russell (2011)</td>
<td>Case series</td>
<td>Four women with previous multiple unsuccessful IVF attempts who fulfilled the criteria for recurrent implantation failure Ultra long pituitary down-regulation was given for at least 6–8 weeks along with prednisolone (15 mg) followed by IVF</td>
<td>MRI and/or USG</td>
<td>Ultra long down-regulation improved the pregnancy rate. All four treatments resulted in pregnancy</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Mijatovic et al. (2010)</td>
<td>Retrospective study</td>
<td>74 infertile women with severe endometriosis who were treated with prolonged down-regulation undergoing IVF/ICSI; 27% had adenomyosis Only 74 of 225 patients were included; mean age: 33 years</td>
<td>USG</td>
<td>There was no difference in outcomes in those with and without adenomyosis</td>
<td>7/11 CASP for case–control studies</td>
</tr>
<tr>
<td>Martínez-Conejero et al. (2011)</td>
<td>Retrospective matched cohort study</td>
<td>152 oocyte recipients with and without adenomyosis; 147 women in control group</td>
<td>TVS or MRI</td>
<td>Implantation was not affected by the presence of adenomyosis but there was higher miscarriage rate leading to lower term pregnancy rates in women with adenomyosis</td>
<td>11/12 CASP for cohort studies</td>
</tr>
<tr>
<td>Costello et al. (2011)</td>
<td>Retrospective cohort study</td>
<td>201 women age ≤42 years with infertility undergoing [IVF/ICSI] treatment between January 2000 and June 2006</td>
<td>TVS</td>
<td>The presence of transvaginal ultrasound diagnosed adenomyosis did not adversely affect outcome in women undergoing IVF/ICSI treatment (both adjusted and unadjusted)</td>
<td>8/12 CASP for cohort studies</td>
</tr>
<tr>
<td>Juang et al., 2007</td>
<td>1:2 nested case–control study</td>
<td>Cohort population of 2138 pregnant women who attended routine prenatal check up between July 199 and June 2005</td>
<td>MRI or USG</td>
<td>Gravid women with adenomyosis were associated with increased risk of both spontaneous preterm delivery (OR, 95% CI 1.84; 1.32–4.31) and PPROM (1.98, 1.39–3.15)</td>
<td>11/11 CASP for case–control studies</td>
</tr>
</tbody>
</table>

USG, ultrasound; TVS, transvaginal scan; HSG, hysterosalpingography.
assessments of the quality of studies included. However, review is compromised by a paucity of good-quality primary studies in all except the diagnosis section. Diagnosis of adenomyosis has number of appropriately conducted studies both for USG and MRI; however, the definitions of the gold standard as well as the test are variable. Other modalities such as CT and uterine muscle biopsy have not been appropriately evaluated. Studies on treatment are limited to case series and a retrospective data without control groups; hence there is significant publication bias.

**Prevalence studies**

Most prevalence studies are from older women undergoing hysterectomy. Hysterectomy is the definitive treatment for adenomyosis but not suitable for women desiring to retain fertility. Apart from one study (Kunz et al., 2005), the included studies have explored only the prevalence of adenomyosis in the symptomatic population rather than in the entire subfertile population. Moreover, limited epidemiological studies of adenomyosis are difficult to interpret because of the varied diagnostic criteria. The available information is insufficient for establishing a cause–effect relationship between adenomyosis and infertility, and hampers any attempt to define incidence and prevalence of the condition and the related risk factors. Another confounding variable is the strong association between adenomyosis and endometriosis. Some authors believe that the two conditions represent different stages of the disease, whereas others identify them as separate entities with one associated with infertility and the other associated with parity.

**Diagnostic studies**

An ideal study testing a predictor of fertility should have a well-defined population, prospective and consecutive recruitment, blinding of those involved in assessing the test results and outcomes and adequate test description, defining normal and abnormal tests before starting the study and comparing it with the gold standard. Most studies exploring diagnostic accuracy included in the review had high scores on the QUADAS scoring system, which supports the validity of their findings. We have used likelihood ratios to determine the usefulness of the diagnostic test because likelihood ratios are most likely to be of clinical relevance, as there are accepted cut-offs for levels of test accuracy. Positive likelihood ratios above 10 and negative likelihood ratios below 0.1 have been noted as providing evidence of high diagnostic accuracy, whereas those above 5 and below 0.2 give evidence of moderate diagnostic accuracy (Jaeschke et al., 1994). Myometrial biopsy had a high positive likelihood ratio; however, there is a wide CI. There was also significant heterogeneity, statistical and clinical, among the three biopsy studies. In addition, biopsy is not an ideal form of diagnosis, as it is an invasive technique.

The non-invasive techniques of MRI and USG have moderate diagnostic values, at best. In this review, both USG and MRI showed similar diagnostic accuracy. USG is routinely available and not expensive, and hence can easily be used in routine clinical practice. However, the criteria for diagnosing adenomyosis have to be agreed. Even on histopathology of the hysterectomy specimen, which is the gold standard for diagnosis, there is a variation in the diagnosis. Most previously published studies have used one low power field as a minimal distance in the diagnostic criteria of adenomyosis; however, large variations have been demonstrated in the area of microscopic fields when using different microscopes. Previous reviews of the accuracy of USG and MRI (Champaneria et al., 2010) and of USG only (Meredith et al., 2009) for diagnosing adenomyosis shows that MRI and USG are good non-invasive tests, with MRI being slightly more accurate. There are variations in the studies included, the way in which the quality of studies was assessed and the conclusions of these reviews.

Champaneria et al. (2010) used arbitrary cut-offs to determine the quality of the study (only 7 out of 14 QUADAS points), on the basis of which some studies were excluded although they were scored as high on QUADAS by Meredith et al. (2009) and ourselves. QUADAS includes items that cover bias, variability and, to a certain extent, the quality of reporting. The majority of items included in QUADAS relate to bias (items 3, 4, 5, 6, 7, 10, 11, 12 and 14), with only two or three items each relating to variability (items 1 and 2) and reporting (items 8, 9 and 13). Hence, we felt that all items were important as bias will limit the validity of the study results, whereas variability may affect the generalizability of study results.

In addition, we have attempted to explore the accuracy of all diagnostic modalities described in the literature (Doppler Hysteroscopy, sonohysterography, CT) and managed to pool the data for biopsy, which none of the other studies have done, thus providing a more comprehensive and up-to-date review. Moreover, unlike the other studies, we have emphasized here that there is no consensus as to how adenomyosis is diagnosed by USG or MRI or even by histopathology.

**Treatment studies**

Although various treatments are advocated and described, there is no definite treatment that can be advocated, primarily because of lack of good quality prospective studies with appropriate control groups. Treatment of adenomyosis in literature is limited to case series and case reports mostly, which have publication bias. Hence, definite conclusions about the efficacy of these treatments are not possible. Therefore, none of these treatments should be offered outside research settings.

**Impact on fertility outcomes**

There are suggestions that adenomyosis is associated with obstetric complications. The evidence to support this comes from a well-conducted appropriately powered case–control study (Juang et al., 2007). There are however conflicting findings of the impact of adenomyosis on assisted reproduction treatment (ART) outcomes, although most retrospective cohort studies, including women using their own oocytes, suggest that there is no detrimental impact of adenomyosis on ART outcome (Table VI). However, there are a wide variations in the population included and in the degree of adenomyosis in these studies. In addition, the presence of endometriosis itself is a confounding factor. Moreover, all studies evaluating the effect of adenomyosis on ART outcomes have given prolonged down-regulation to all women in the study, which is suggested as one of the treatment for women with adenomyosis undergoing ART. It is uncertain whether this masks the effect of adenomyosis and whether or not it should be recommended as a treatment in these women.
Implications for clinical practice

Although adenomyosis can be diagnosed during various investigations for infertility, its significance is uncertain with respect to infertility or outcomes after ART. Additionally, the diagnostic tests need standardization. In cases of unexplained infertility, although both patients as well as clinicians are looking for a diagnosis, there is no indication for diagnosing or treating adenomyosis, at present.

Implications for research

It is likely that adenomyosis will be diagnosed more frequently in subfertile women in the future because of increased awareness, women delaying pregnancy to a later age and better diagnostic facilities. We therefore need good-quality epidemiological studies to identify the natural history of adenomyosis, to explore its effect on fertility and to determine the effectiveness of fertility sparing treatments. New conservative treatments need to be evaluated by well-powered randomized controlled trials before these are incorporated within routine clinical practice. However, before that, we need an agreement on criteria for diagnosis by various modalities.

Conclusion

Adenomyosis is present in a high proportion of women with subfertility, particularly those with endometriosis and or symptoms suggestive of adenomyosis and dysmenorrhea. MRI and USG are non-invasive diagnostic tests with a similar accuracy in diagnosing adenomyosis. However, the criterion for diagnosing adenomyosis needs to be agreed on.

There are no fertility-sparing treatments of proven effectiveness. Various treatments that have been advocated need testing in large, well-designed, adequately powered studies. How much the diagnosis of adenomyosis has an impact on success rate of treatment or spontaneous conception is not known. However, with more women delaying pregnancy and with better diagnostic facilities, more women will be diagnosed with adenomyosis; hence more studies are needed to determine its implications on reproductive outcomes, with and without treatment. Until then, there is no indication for finding or treating adenomyosis in women who wish to conceive.

Supplementary data

Supplementary data are available at http://humupd.oxfordjournals.org/

Authors’ roles

A.M. conceptualized the idea and did the initial searches. F.F. and S.G. also did the searches. S.G. and A.M. performed data entry and quality assessment. S.G. wrote the initial version and A.M. finalized the initial version of the manuscript. S.B. provided intellectual input at all stages.

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