Uterine adenomyosis and in vitro fertilization outcome: a systematic review and meta-analysis

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**STUDY QUESTION:** Is adenomyosis associated with IVF/ICSI outcome in terms of clinical pregnancy rate?

**SUMMARY ANSWER:** In a meta-analysis of published data, women with adenomyosis had a 28% reduction in the likelihood of clinical pregnancy at IVF/ICSI compared with women without adenomyosis.

**WHAT IS KNOWN ALREADY:** Estimates of the effect of adenomyosis on IVF/ICSI outcome are inconsistent.

**STUDY DESIGN, SIZE, DURATION:** A systematic literature review and meta-analysis were conducted. A Medline search was performed to identify all the comparative studies published from January 1998 to June 2013 in the English language literature on IVF/ICSI outcome in women with and without adenomyosis. Two authors independently performed the literature screening, scrutinized articles of potential interest, selected relevant studies and extracted data. Studies were categorized based on research design.

**PARTICIPANTS, SETTING, METHODS:** Of the 17 articles assessed in detail, 9 were finally selected based on diagnosis of adenomyosis at magnetic resonance imaging or transvaginal ultrasonography. The quality of studies was evaluated by means of the Newcastle-Ottawa scale. A total of 1865 women were enrolled in the 9 selected studies, 665 of whom in 4 prospective observational studies, and 1200 in 5 retrospective studies. The dichotomous data for clinical pregnancy and secondary outcomes were expressed as risk ratios (RR) with 95% confidence intervals (CIs) and were combined in a meta-analysis using the random-effects model. The heterogeneity Cochrane’s Q and the $I^2$ statistics were calculated.

**MAIN RESULTS AND THE ROLE OF CHANCE:** The clinical pregnancy rate achieved after IVF/ICSI was 123/304 (40.5%) women with adenomyosis versus 628/1262 (49.8%) in those without adenomyosis. The RR of clinical pregnancy ranged from 0.37 (95% CI, 0.15–0.92) to 1.20 (95% CI, 0.58–2.45), with a significant heterogeneity among studies ($I^2 = 56.8\%, P = 0.023$). Pooling of the results yielded a common RR of 0.72 (95% CI, 0.55–0.95). A funnel plot showed no indication of asymmetry among studies (Egger’s test, $P = 0.696$). In a meta-regression model, no association was observed between prevalence of endometriosis and the likelihood of clinical pregnancy. Three studies reported the pregnancy rate per cycle. The common RR was 0.71 (95% CI, 0.51–0.98; $I^2 = 78.1\%, P = 0.010$). The RR observed in a study with donated oocytes was 0.90 (95% CI, 0.75–1.08). The number of miscarriages per clinical pregnancy was reported in seven studies. A miscarriage was observed in 77/241 women with adenomyosis (31.9%) and in 97/687 in those without adenomyosis (14.1%). The RR of miscarriage ranged from 0.57 (95% CI, 0.15–2.17) to 18.00 (95% CI, 4.08–79.47; $I^2 = 67.7\%, P = 0.005$). Pooling of the results yielded a common RR of 2.12 (95% CI, 1.20–3.75).

**LIMITATIONS, REASONS FOR CAUTION:** Qualitative and quantitative heterogeneity among studies was high. At sensitivity analysis, $I^2$ statistic regarding the main outcome was reduced under the 50% threshold removing one trial, but the resulting confidence interval crossed unity. Also the confidence interval of the common RR of the four studies reporting only one IVF/ICSI cycle included unity. Only part of the studies could be included in the assessment of secondary outcomes.

**WIDER IMPLICATIONS OF THE FINDINGS:** Adenomyosis appears to impact negatively on IVF/ICSI outcome owing to reduced likelihood of clinical pregnancy and implantation, and increased risk of early pregnancy loss. Screening for adenomyosis before embarking on medically...
A causal relation between adenomyosis and infertility has been repeatedly suggested (Matalliotakis et al., 2005; Leyendecker et al., 2006; Brosens et al., 2010; Campo et al., 2012a; Sunkara and Khan, 2012; Tomassetti et al., 2013), but definitive demonstrations are still lacking. The reported prevalence of adenomyosis in the infertile population varies widely (Maheshwari et al., 2010; Campo et al., 2012a; Thalluri and Tremellen, 2012) and recently published figures (Naftalin et al., 2012; Thalluri and Tremellen, 2012) are similar to those observed in the general population (Vercellini et al., 1995; Parazzini et al., 1997). The inconsistent literature findings regarding the effect of adenomyosis on fertility may be partly explained by differences in the diagnostic criteria adopted (Vercellini et al., 2006). Moreover, medical cure of adenomyosis seems unrealistic, whereas excision of adenomyotic lesions is sometimes pursued, but usually in case of advanced forms (Grimbizis et al., 2013). Thus, data on a potential effect of adenomyosis on reproductive performance are difficult to derive from randomized interventional trials.

In general, as women delay seeking conception, adenomyosis should be encountered more and more often among infertile women, and in particular among those who access IVF and ICSI programmes (Devlieger et al., 2003). Indeed, uterine morphology should be examined carefully before resorting to assisted reproductive techniques, and nowadays a reliable, non-invasive diagnosis is possible using transvaginal ultrasonography (TVUS) and magnetic resonance imaging (MRI) (Dueholm and Lundorf, 2007). The two modalities have demonstrated similar good overall test performance (Meredith et al., 2009; Maheshwari et al., 2012).

In recent years, several studies assessed IVF outcome in women with and without adenomyosis, but the results are inconsistent. Therefore, we deemed it of interest to conduct a systematic literature review and meta-analysis of data published in the last 15 years, with the objective of defining more precisely the effect of adenomyosis on the probability of pregnancy at IVF/ICSI. Combining the evidence on this controversial issue may reveal useful information for patient counselling, and may clarify if screening for adenomyosis is indicated before recommending IVF/ICSI. Moreover, pooling the results of the available evidence may also indirectly help disentangling the uncertainties surrounding the relation between this condition and fertility in general.

The primary outcome of interest of this systematic review and meta-analysis was clinical pregnancy rate per patient (number of pregnancies per total number of subjects undergoing IVF/ICSI) in women with or without adenomyosis. Secondary outcomes of interest were clinical pregnancy rate per cycle (number of pregnancies per number of IVF/ICSI cycles), implantation rate per cycle (number of gestational sacs per number of embryos transferred), miscarriage rate per clinical pregnancy (number of miscarriages per number of clinical pregnancies), live birth rate per patient (number of live births per total number of subjects undergoing IVF/ICSI), and comparison of success rates in women undergoing IVF/ICSI after a long versus short down-regulation protocol, as well as in those with a MRI versus TVUS diagnosis of adenomyosis. The impact of study design (prospective versus retrospective) and of endometriosis prevalence were also investigated.

### Materials and Methods

The present literature overview was conducted according to the PRISMA guidelines for systematic reviews (Moher et al., 2009). As published de-identified data were used, the present study was exempt from Institutional Review Board approval.

### Sources

This review was restricted to published research articles that compared the pregnancy rate after IVF/ICSI in infertile women with adenomyosis identified at TVUS and/or pelvic MRI, with that observed in women without adenomyosis. Several different strategies were adopted to identify medical papers published on the effect of adenomyosis on IVF/ICSI outcome. The primary search was conducted with Medline including the time period from January 1998 to June 2013, and using combinations of the medical subject heading terms ‘adenomyosis’, ‘infertility’, ‘in-vitro fertilisation’, ‘intracytoplasmic sperm injection’, ‘endometriosis’, ‘pregnancy’, and ‘miscarriage’. Only those publications written in English were included. Abstracts of scientific meetings and conference proceedings were not considered. All pertinent articles were retrieved and the relative reference lists were systematically reviewed in order to identify further reports that could be included in the meta-analysis. Moreover, review articles published on adenomyosis in the same time-span were consulted and their reference lists searched for potential additional studies. No attempt was made to identify unpublished studies.

### Study selection

Two authors (B.B. and D.D.) independently performed an initial screening of the title and abstract of all articles to exclude citations deemed irrelevant by both observers (e.g. if only women with adenomyosis were described without a comparison group of women without adenomyosis; if treatment included surgical resection of adenomyosis before IVF/ICSI; or if other assisted reproductive techniques other than IVF/ICSI were used). Original articles were selected based on description of diagnostic modalities of adenomyosis at TVUS and/or MRI, definition of infertility status, and description of the control population. Reports on the effect of adenomyosis on pregnancy rate after complex surgery, including colorectal resection, for advanced deep endometriosis were excluded.

The quality of studies was evaluated by means of the Newcastle-Ottawa scale, a validated modality for assessing observational and non-randomized studies (Wells et al., 2000). The scale uses a score system based on three major criteria: selection of participants, comparability of study groups and assessment of exposure. The quality checklist includes eight items with a score of 0, 1 or 2 can be awarded. Therefore, the quantitative appraisal of overall quality of the individual studies ranged from 0 to 9. No cut-off level was set for inclusion in the meta-analysis.
Data extraction and analysis

Studies were categorized based on research design. The year of publication, location, setting, number and clinical characteristics of recruited subjects, modality of diagnosis of adenomyosis, description of down-regulation protocol, and number of IVF/ICSI cycles performed in the two study groups were recorded. The number of patients who achieved a clinical pregnancy in the group of women with and without adenomyosis was obtained from individual reports. The two observers independently evaluated all articles and abstracted data unto standardized forms. In cases where data were missing, insufficient or unclear, further information was sought from the original study investigators who were contacted by e-mail. A final extraction form was compiled from the two evaluation forms, with correction or resolution of any discrepancies between reviewers by consensus reached after discussion, or arbitration by a third reviewer (P.V.).

Irrespective of the method used in the original papers, the results for clinical pregnancy and secondary outcomes were expressed as risk ratios (RR) with 95% confidence intervals (CIs) (Egger et al., 2001). The RR were combined in a meta-analysis using a fixed-effects model when heterogeneity observed among studies was absent to moderate, or the DerSimonian and Laird method (DerSimonian and Laird, 1986; DerSimonian and Kacker, 2007) for a random-effects model, when heterogeneity was high ($I^2 \geq 50\%$) (Egger et al., 2001). A meta-regression model was fitted to assess the relationship between endometriosis prevalence and likelihood of clinical pregnancy (Egger et al., 2001). When assessing the summary graphs, the outcome of clinical pregnancy was a positive effect, and a higher pregnancy rate was considered a benefit. The outcome of miscarriage was a negative effect, and a higher number was considered harmful.

The heterogeneity Cochrane $Q$ and the $I^2$ statistics, which describe the proportion of the total variation of estimates across studies due to heterogeneity rather than chance (Higgins et al., 2003), were then calculated. Negative values of $I^2$ are set equal to 0 so that $I^2$ lies between 0 and 100%. A value of 0% indicates no observed heterogeneity, whereas $I^2$ values of 25, 50 and 75% indicate low, moderate and high heterogeneity, respectively (Higgins et al., 2003). If $I^2$ was $\geq 50\%$, sensitivity analyses were conducted to verify if any one study unduly influenced the pooled effect size.

Funnel plots, which graph RR on a log scale (effect) against standard error of log-RR (precision), were generated and visually inspected for asymmetry to determine if the included studies were non-representative of the body of possible studies on the subject (which could result from small study effect or other biases, such as publication and poor-quality bias). Egger’s approach to testing the significance of funnel plot asymmetry was also used (Egger et al., 1997). All analyses were performed using Stata, version 13 (StataCorp 2013, TX, USA).

Results

Figure 1 shows the flow diagram of the literature search results. The Medline search identified 154 records. Another 12 citations were found from search of reference lists. A total of 148 publications were excluded because it was clear from the abstract that they did not fulfil the selection criteria. We obtained full manuscripts of the remaining 18 articles. We excluded four publications (Wood 2001; Brosens et al., 2004, 2013; Maheshwari et al., 2012) as no original data were reported; two (Darai et al., 2005, 2010) because fertility outcome was assessed after colorectal resection for endometriosis; one (Tremellen and Russell, 2012) because no data on IVF outcome were reported; one (Kunz and Beil, 2010) because it was not possible to extract the number of women who achieved a conception by means of IVF in separate groups with or without adenomyosis; and one (Tremellen and Russell, 2011) because no control group was considered.

Data on the effect of adenomyosis on clinical pregnancy rate after IVF/ICSI were extracted from the remaining 9 articles, all of which were published in full in peer-reviewed journals between 1999 and 2012 (Chiang et al., 1999; Maubon et al., 2010; Mijatovic et al., 2010; Costello et al., 2011; Martínez-Concejero et al., 2011; Youm et al., 2011; Ballester et al., 2012; Salim et al., 2012; Thalluri and Tremellen, 2012). Complete reviewers’ agreement regarding inclusion and exclusion of studies was achieved in six instances. In one prospective study (Maubon et al., 2010) there was no precise definition of diagnosis of adenomyosis at MRI, although IVF outcome was categorized based on different combinations of uterine junctional zone thickness threshold values measured at pelvic MRI (average junctional zone thickness $\leq 7$ versus $>7$ mm, and maximal junctional zone thickness $\leq 10$ versus $>10$ mm). After arbitration by the third reviewer, it was decided to include the study considering as adenomyosis cases only those with a threshold value of $>7$ mm for average junctional zone thickness. Similarly, in the study by Youm et al. (2011) results were stratified based on maximum myometrial thickness ($<2.00$, $2.00–2.49$, $2.50$ cm). This study was included considering as adenomyosis cases only those with a threshold value of $>2.0$ cm for maximum myometrial thickness, thus combining data relative to the latter two groups. In another study only women participating in an oocyte-donation programme were considered (Martínez-Concejero et al., 2011). Moreover, outcome was reported only in terms of pregnancy rate per cycle and it was not possible to calculate the rate per patient. It was decided to include this study only in the analyses on pregnancy rate per cycle and miscarriage rate per clinical pregnancy, even if only the uterine component was investigated. In addition, two control groups were considered, ‘endometriosis’, and ‘no adenomyosis/endometriosis’. Because it was unclear if and to what extent adenomyosis was present in women in the ‘endometriosis’ category, it was decided to specifically exclude this group from the analysis and to consider only women in the ‘adenomyosis’ and ‘no adenomyosis/endometriosis’ categories.

Details of the characteristics of the selected studies are shown in Table I. All included studies were observational studies, four of which were prospective cohort studies (Chiang et al., 1999; Maubon et al., 2010; Ballester et al., 2012; Salim et al., 2012), and five retrospective cohort studies (Mijatovic et al., 2010; Costello et al., 2011; Martínez-Concejero et al., 2011; Youm et al., 2011; Thalluri and Tremellen, 2012). Two studies were conducted in France (Maubon et al., 2010; Ballester et al., 2012), two in Australia (Costello et al., 2011; Thalluri and Tremellen, 2012), one in the Netherlands (Mijatovic et al., 2010), one in Spain (Martínez-Concejero et al., 2011), one in the Republic of Korea (Youm et al., 2011), one in Taiwan (Chiang et al., 1999) and one in the UK (Salim et al., 2012). A total of 1865 women were enrolled, 456 with and 1409 without adenomyosis. The prevalence of adenomyosis in the infertility population undergoing IVF/ICSI varied widely, from 6.9% (Salim et al., 2010) to 34.3% (Martínez-Concejero et al., 2011), with a mean $\pm$ SD value of $21.9 \pm 8.8\%$. A total of 665 women were recruited in prospective cohort studies, and 1200 in retrospective cohort studies. The reported maximum age at IVF of recruited women was 43 years (Maubon et al., 2010), but in most studies the age limit was 42 (Costello et al., 2011; Martínez-Concejero et al., 2011; Ballester et al., 2012), or lower (Youm et al., 2011, 40 years; Thalluri and Tremellen, 2012, 39 years). In one study the age limit was not specified (Chiang et al., 1999), but the mean $\pm$ SD age of the patients was $36.0 \pm 2.6$ years. Adenomyosis was diagnosed at MRI in two studies (Maubon...
et al., 2010; Ballester et al., 2012), and at TVUS in seven (Chiang et al., 1999; Mijatovic et al., 2010; Costello et al., 2011; Martínez-Conejero et al., 2011; Youm et al., 2011; Salim et al., 2012; Thalluri and Tremellen, 2012).

Only women with a concomitant diagnosis of endometriosis were included in two studies (Mijatovic et al., 2010; Ballester et al., 2012), whereas in other six studies a variable proportion of women with a diagnosis of endometriosis were included (Maubon et al., 2010, 54/152 = 35.5%; Costello et al., 2011, 21/201 = 10.4%; Martínez-Conejero et al., 2011, 23/152 = 15.1%; Youm et al., 2011, 57/413 = 13.8%; Salim et al., 2012, 22/275 = 8.0%; Thalluri and Tremellen, 2012, 5/213, 2.3%). However, it was not always formally stated if all women underwent laparoscopy (e.g. it appears that women included in the study by Thalluri and Tremellen (2012) did not undergo direct pelvic visualization). In one study (Chiang et al., 1999), no mention was made of either laparoscopy performance or a previous diagnosis of endometriosis. Even when the number of women with endometriosis was indicated, it was not always stated if lesions were systematically treated, how, and to what extent. More importantly, it was not possible to assess the distribution of conceptions between distinct groups of women with adenomyosis plus endometriosis or adenomyosis without endometriosis.

Only one IVF/ICSI cycle was considered in four studies (Mijatovic et al., 2010; Costello et al., 2011; Salim et al., 2012; Thalluri and Tremellen, 2012), and more than one in four studies (Maubon et al., 2010; Martínez-Conejero et al., 2011; Youm et al., 2011; Ballester et al., 2012). In one study (Chiang et al., 1999) the number of cycles was not specified. In two studies a long GnRH agonist down-regulation was used (Mijatovic et al., 2010; Costello et al., 2011), whereas in four studies a short protocol was adopted (Maubon et al., 2010; Youm et al., 2011; Salim et al., 2012; Thalluri and Tremellen, 2012). Both long or short GnRH agonist down-regulation protocols were used in one study (Chiang et al., 1999), and a mixed use of GnRH agonists or antagonists for various periods of time was reported in another one (Ballester et al., 2012). The definition of clinical pregnancy was based on ultrasonographic demonstration of an intrauterine embryo with fetal heart activity in four studies (Mijatovic et al., 2010; Costello et al., 2011; Youm et al., 2011; Salim et al., 2012), or on presence of an intrauterine sac at TVUS.
<table>
<thead>
<tr>
<th>Source</th>
<th>Year</th>
<th>Country</th>
<th>Study population</th>
<th>Study design</th>
<th>Diagnostic criteria</th>
<th>No. of women with adenomyosis</th>
<th>No. of women without adenomyosis</th>
<th>IVF protocol details</th>
<th>No. of IVF/ICSI cycles</th>
<th>Quality of evidence&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chiang et al.</td>
<td>1999</td>
<td>Taiwan</td>
<td>Infertile women undergoing TVUS prior to IVF; mean age, 36 years; causes of infertility not reported</td>
<td>Prospective cohort study</td>
<td>TVUS: diffusely enlarged uterus without distinct uterine masses, ≥1 heterogeneous and not encapsulated myometrial areas, with round, 1–3 mm, anechoic areas</td>
<td>19</td>
<td>144</td>
<td>Short-term or long-term down-regulation with GnRH agonists</td>
<td>NR</td>
<td>6</td>
</tr>
<tr>
<td>Maubon et al.</td>
<td>2010</td>
<td>France</td>
<td>Infertile women undergoing a pelvic MRI prior to IVF attempt; mean age, 33 years (21–43); various causes of infertility</td>
<td>Prospective cohort study</td>
<td>Pelvic MRI with definition of average (&lt; or &gt;7 mm) and maximal (&lt; or &gt;10 mm) junctional zone</td>
<td>39&lt;sup&gt;b&lt;/sup&gt;</td>
<td>113</td>
<td>Short-term down-regulation with GnRH agonists or antagonists</td>
<td>≥1</td>
<td>6</td>
</tr>
<tr>
<td>Mijatovic et al.</td>
<td>2010</td>
<td>Netherlands</td>
<td>Infertile women with surgically proven endometriosis, screened for adenomyosis by TVUS, undergoing their first IVF cycle after long-term GnRH agonist treatment; mean age 33 years</td>
<td>Retrospective cohort study</td>
<td>TVUS: asymmetry of uterine walls, myometrial areas of heterogeneous echogenicity, small myometrial cysts</td>
<td>20</td>
<td>54</td>
<td>Long-term (&gt;3 months) GnRH agonist down-regulation; no more than 2 embryos transferred</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Costello et al.</td>
<td>2011</td>
<td>Australia</td>
<td>Infertile women undergoing one IVF/ICSI cycle, screened for adenomyosis by TVUS; age &lt;42 years (18–42); various causes of infertility</td>
<td>Retrospective cohort study</td>
<td>TVUS: asymmetrically thickened myometrium between anterior and posterior walls, myometrial cysts and poor definition of endometrial-myometrial junction</td>
<td>37</td>
<td>164</td>
<td>Long-term GnRH agonist down-regulation</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Martinez-Conejero et al.</td>
<td>2011</td>
<td>Spain</td>
<td>Infertile women screened for adenomyosis by TVUS, undergoing oocyte donation cycles; age 39–42 years. Women with fibroids or other anomalies identified at TVUS excluded.</td>
<td>Retrospective cohort study</td>
<td>TVUS: hypoechoic and heterogeneous areas with decreased echogenicity, elliptic intramyometrial lakes &gt;2 mm in a globular-appearing uterus</td>
<td>152</td>
<td>147&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Oocytes donation programme</td>
<td>2 (1–11)</td>
<td>7</td>
</tr>
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</table>

<sup>a</sup> Quality of evidence is based on the methodology and outcomes reported in each study.
| Study: Youm et al. 2011 | Rep. of Korea | Infertile women undergoing IVF for various reasons; women with myomas, poor responders, cases with male factor infertility were excluded; age ≤ 40 years | Retrospective cohort study | TVUS: myometrial thickening, striations, heterogeneity, cysts and poorly defined endometrial-myometrial junction | 111d | 302 | Short-term GnRH agonist down-regulation | 1–2 | 7 |
| Study: Ballester et al. 2012 | France | Infertile women with colorectal endometriosis, identified by TV sonography and MRI, screened for adenomyosis by TVUS; mean age 33 years (23–42) | Prospective cohort multicentre study | Pelvic MRI: maximal junctional zone thickness of at least 12 mm; ratio $JZ_{\text{max}}/\text{myometrial thickness} > 40\%$; punctate high-density myometrial foci | 21 | 54 | Long down-regulation with GnRH agonist or short agonist or antagonist protocol | 1–3 | 5 |
| Study: Salim et al. 2012 | UK | Infertile women with adequate ovarian reserve undergoing their first IVF/ICSI cycle, screened for adenomyosis by TVUS; women with fibroids or a previous myomectomy were excluded; mean age 34 years | Prospective cohort study | TVUS: asymmetrical thickening of the myometrium, irregular cystic areas within the myometrium, linear striations radiating out from the myometrium | 19 | 256 | Short-term GnRH agonist down-regulation; 1–3 embryos transferred (mean = 2) | 1 | 6 |
| Study: Thalluri and Tremellen 2012 | Australia | Infertile women undergoing IVF cycle with single transfer of a good quality embryo (grade 1 or 2), screened for adenomyosis by TVUS and no additional pelvic pathology that may impact on IVF success (fibroids, hydrosalpinx, endometriomas or endometrial polyps); age ≤ 39 years | Retrospective cohort study | TVUS: enlarged globular uterus, asymmetric thickening of myometrial walls, heterogeneous, poorly circumscribed areas within the myometrium, anechoic myometrial blood filled lacunae or cysts of varying size, increased echo-texture of the endometrium, and sub-endometrial linear striations | 38 | 175 | GnRH antagonist stimulation followed by transfer of a solitary good quality embryo (grade 1 or 2) on Day 4/5 | 1 | 7 |

TVUS, transvaginal ultrasonography; MRI, magnetic resonance imaging; NR, not reported.

a Based on the Newcastle-Ottawa scale (Wells et al., 2000).
b Categorized based on average junctional zone $> 7$ mm.
c Only women without anomalies are considered (endometriosis group excluded).
d All women with maximum myometrial thickness $\geq 2$ cm are considered.
performed during the fifth (Ballester et al. 2012) or eighth gestational week (Thalluri and Tremellen, 2012). In two studies the week of gestation was not specified (Chiang et al., 1999; Maubon et al., 2010), and in another one a definition for clinical pregnancy was not reported (Martinez-Conejero et al., 2011).

The authors of four studies (Maubon et al., 2010; Mijatovic et al., 2010; Martinez-Conejero et al., 2011; Ballester et al., 2012) were contacted by e-mails in order to obtain additional information, and clarification of some data was obtained from co-authors of the study by Martinez-Conejero et al., and from Ballester.

The quality score of the considered studies ranged from 5 to 8 and the average score (Mean ± SD) for all nine studies was 6.4 ± 0.9. In eight studies (Chiang et al., 1999; Maubon et al., 2010; Mijatovic et al., 2010; Costello et al., 2011; Martinez-Conejero et al., 2011; Youm et al., 2011; Salim et al., 2012; Thalluri and Tremellen, 2012) there was adequate selection of women with and without adenomyosis. In one study (Ballester et al., 2012) subjects in the adenomyosis and no adenomyosis categories were probably not largely representative of the source populations, as severe, infiltrating endometriosis with colorectal involvement was the main selection criteria for both cohorts. Ascertainment of presence of adenomyosis was adequate in all studies as it was based on validated TVUS or MRI imaging criteria. The same was true for demonstration that the outcome of interest (pregnancy) was not present at start of study. The overall performance on comparability of participants was fair in six studies (Chiang et al., 1999; Maubon et al., 2010; Mijatovic et al., 2010; Martinez-Conejero et al., 2011; Youm et al., 2011; Salim et al., 2012), and adequate in three in which potential confounders were controlled (Costello et al., 2011; Ballester et al., 2012; Thalluri and Tremellen, 2012). Assessment of outcome was based on standardized criteria in eight studies (Chiang et al., 1999; Maubon et al., 2010; Mijatovic et al., 2010; Costello et al., 2011; Youm et al., 2011; Ballester et al., 2012; Salim et al., 2012; Thalluri and Tremellen, 2012). In one study (Martinez-Conejero et al., 2011) no definition was specified for the determination of clinical pregnancy. Duration of follow-up was extended until birth in four studies (Chiang et al., 1999; Costello et al., 2011; Martinez-Conejero et al., 2011; Youm et al., 2011). In none of the studies it was possible to ascertain whether losses to follow-up occurred.

In order to define the overall effect of adenomyosis on pregnancy rate per patient, all the women with the condition were compared with all control subjects (with the exception of the study by Martinez-Conejero et al. (2011) in which only pregnancy rates per cycle were reported), independently of type of diagnostic modality, pharmacological preparation (short versus long protocol) and study design.

A clinical pregnancy was achieved after IVF/ICSI in 123/304 (40.5%) women with adenomyosis and in 628/1262 (49.8%) in those without adenomyosis. The RR of clinical pregnancy ranged from 0.37 (95% CI, 0.15–0.92; Ballester et al., 2012) to 1.20 (95% CI, 0.58–2.45; Chiang et al., 1999), with a significant heterogeneity among the studies ($I^2 = 56.8\%$, $P = 0.023$). Therefore, the DerSimonian–Laird random-effects model was used to compute the overall RR. Pooling of the results derived from the eight included studies yielded a common RR of 0.72 (95% CI, 0.55–0.95), demonstrating that adenomyosis was associated with a 28% reduction in the likelihood of clinical pregnancy in infertile women undergoing IVF/ICSI (Fig. 2).

A funnel plot showed no indication of asymmetry among studies (Egger’s test, $P = 0.43$; Supplementary data, Fig. S1). At sensitivity analysis, the common RR varied from 0.67 (95% CI, 0.49–0.91) excluding the study by Costello et al. (2011), to 0.80 (95% CI, 0.62–1.02) excluding the study by Maubon et al. (2010). Removal of studies one at a time from the meta-analysis suggested that the trial by Maubon et al. (2010) was a source of quantitative variation and that it may have influenced the pooled estimate. In fact, the exclusion of this study reduced between-study heterogeneity ($I^2 = 39.7\%$; $P = 0.127$).

Only three studies reported the pregnancy rate per cycle (Maubon et al., 2010; Martinez-Conejero et al., 2011; Youm et al., 2011). In the study by Ballester et al. (2012) some women underwent more than one cycle, but it was not possible to extrapolate crude numbers in the subgroups with and without adenomyosis. In four studies (Mijatovic et al., 2010; Costello et al., 2011; Salim et al., 2012; Thalluri and Tremellen, 2012) only one IVF/ICSI cycle was considered. The common RR of the three studies reporting pregnancy rate per cycle (Maubon et al., 2010; Martinez-Conejero et al., 2011; Youm et al., 2011) was 0.71 (95% CI, 0.51–0.98; $I^2 = 78.1\%$, $P = 0.010$). The RR observed in the study by Martinez-Conejero et al. (2011) with donated oocytes was 0.90 (95% CI, 0.75–1.08). A funnel plot showed no indication of asymmetry among studies (Egger’s test, $P = 0.291$). The common RR of the four studies reporting only one IVF/ICSI cycle was 0.80 (95% CI, 0.53–1.20; Supplementary data, Fig. S2).

Implantation rate per cycle with crude numbers relative to gestational sacs per embryos transferred was reported in three studies (Costello et al., 2011, 2012). The RR of implantation varied from 0.64 (95% CI, 0.31–1.33; Salim et al., 2012) to 0.90 (95% CI, 0.56–1.44; Costello et al., 2011), with absence of heterogeneity among the studies ($I^2 = 0.0\%$, $P = 0.718$). Pooling of the results adopting a fixed effects model yielded a common RR of 0.77 (95% CI, 0.63–0.93; Supplementary data, Fig. S3). Two studies reported only percentages without crude numbers. The implantation rate per cycle in women with and without adenomyosis was, respectively, 31.0 and 28.2% in the study by Mijatovic et al. (2010), and 29.6 and 30.8% in the study by Martinez-Conejero et al. (2011).

The number of miscarriages per clinical pregnancy was reported in seven studies (Chiang et al., 1999; Mijatovic et al., 2010; Costello et al., 2011; Martinez-Conejero et al., 2011; Youm et al., 2011; Salim et al., 2012; Thalluri and Tremellen, 2012). A miscarriage was observed in 77/241 pregnancies in women with adenomyosis (31.9%) and in 97/687 in those without adenomyosis (14.1%). The RR of miscarriage ranged from 0.57 (95% CI, 0.15–2.17; Costello et al., 2011) to 18.00 (95% CI, 4.08–79.47; Salim et al., 2012), with a significant heterogeneity among the studies ($I^2 = 67.7\%$, $P = 0.005$). Pooling of the results using the DerSimonian–Laird random-effects model yielded a common RR of 2.12 (95% CI, 1.20–3.75), suggesting that adenomyosis was associated with an increased risk of miscarriage (Fig. 3). The RR in the study by Martinez-Conejero et al. (2011), in which donated oocytes were used, was similar to the overall estimate (RR, 2.01; 95% CI, 1.29–3.12). The funnel plot showed no indication of asymmetry among studies (Egger’s test, $P = 0.90$; Supplementary data, Fig. S4).

At sensitivity analysis, the common RR varied from 1.78 (95% CI, 1.23–2.80) excluding the study by Salim et al. (2012), to 2.53 (95% CI, 1.43–4.48) excluding the study by Mijatovic et al. (2010). Removal of studies one at a time from the meta-analysis suggested that the trial by Salim et al. (2012) was a source of quantitative variation and that it may have influenced the pooled estimate. In fact, the exclusion of this study reduced between-study heterogeneity ($I^2 = 49.6\%$, $P = 0.077$).
Live birth rate with crude numbers was reported in three studies (Chiang et al., 1999; Costello et al., 2011; Youm et al., 2011), with a Mantel–Haenszel pooled RR of 0.70 (95% CI, 0.56–0.87; $I^2 = 44.2%$, $P = 0.166$; Supplementary data, Fig. S5). Martínez-Conejero et al. (2011) reported a live birth rate per cycle of 26.8% (88/328) in the adenomyosis group and of 37.1% (123/331) in the no adenomyosis group. The difference was statistically significant.

The common RR of clinical pregnancy per patient was 1.05 (95% CI, 0.75–1.48; $I^2 = 0.0%$, $P = 0.698$) in the two studies in which a long protocol was adopted (Mijatovic et al., 2010; Costello et al., 2011), whereas it was 0.58 (95% CI, 0.38–0.88) after pooling data from the four studies in which a short GnRH agonist down-regulation was used (Maubon et al., 2010; Youm et al., 2011; Salim et al., 2012; Thalluri and Tremellen, 2012) (Fig. 4).

Two studies used MRI for diagnosis (Maubon et al., 2010; Ballester et al., 2012), with a common RR of clinical pregnancy per patient of 0.40 (95% CI, 0.25–0.64; $I^2 = 0.0%$, $P = 0.847$). The corresponding figure after pooling the results of the remaining six studies in which TVUS was used for diagnosis (Chiang et al., 1999; Mijatovic et al., 2010; Costello et al., 2011; Youm et al., 2011; Salim et al., 2012; Thalluri and Tremellen, 2012) was 0.84 (95% CI, 0.68–1.04; $I^2 = 26.1%$, $P = 0.239$; Fig. 5).

We analysed separately prospective and retrospective trials. The overall RR of clinical pregnancy per patient observed in the four prospective studies (Chiang et al., 1999; Maubon et al., 2010; Ballester et al., 2012; Salim et al., 2012) was 0.55 (95% CI, 0.32–0.96; $I^2 = 54.4%$, $P = 0.087$), whereas it was 0.84 (95% CI, 0.67–1.06; $I^2 = 32.0%$, $P = 0.220$) in the four retrospective ones (Mijatovic et al., 2010; Costello et al., 2011; Youm et al., 2011; Thalluri and Tremellen, 2012; Fig. 6).

Finally, in a meta-regression model, no association was observed between prevalence of endometriosis and the likelihood of clinical pregnancy. Moreover, when combining the studies by Mijatovic et al. (2010) and Ballester et al. (2012) in which only women with a concomitant diagnosis of endometriosis were included, a clinical pregnancy was achieved after IVF/ICSI in 15/41 (36.6%) women with adenomyosis and in 58/108 (53.7%) in those without adenomyosis, with a common RR of 0.65 (95% CI, 0.23–1.84; $I^2 = 76.3%$, $P = 0.040$). On the other hand, the findings of the two studies with the lower prevalence of concomitant endometriosis (Salim et al., 2012, 8.0%; Thalluri and Tremellen, 2012, 2.3%) still demonstrated a greatly reduced likelihood of clinical pregnancy after IVF/ICSI in the adenomyosis group (13/57 = 22.8%) compared with the no-adenomyosis group (186/431 = 43.2%; common RR, 0.52 (95% CI, 0.32–0.85; $I^2 = 0.0%$, $P = 0.908$).

**Discussion**

In the present meta-analysis, adenomyosis was associated with a 28% (95% CI, 5–45%) reduction in the likelihood of clinical pregnancy in infertile women who underwent IVF/ICSI with autologous oocytes. A similar detrimental effect was observed when the number of IVF/ICSI cycles was chosen as denominator (pregnancy rate per cycle). However, the difference in pregnancy rate between women with or without adenomyosis was no longer statistically significant when selecting studies in which women underwent only one IVF/ICSI cycle. These overall estimates should be considered with caution. Quantitative heterogeneity among studies was high and, in the general analysis, it was reduced below the 50% threshold only by excluding the study by Maubon et al. (2010). However, the upper 95% confidence limit of the resulting pooled estimate (RR = 0.80) was slightly above unity (1.02).
Considerations on implantation rate are limited by the fact that crude numbers were reported in only three studies (Costello et al., 2011; Youm et al., 2011; Salim et al., 2012), and that the overall estimate is not consistent with the results of other two studies in which merely percentages were reported (Mijatovic et al., 2010; Martinez-Conejero et al., 2011).

Adenomyosis was also associated with a more than doubled risk of miscarriage, thus suggesting a causal relation. The 95% confidence interval for the increase in risk among women with characteristics comparable to the study population is between 20 and 275%. In this regard, the study by Martinez-Conejero et al. (2011) appears particularly interesting, as the use of donated oocytes allows the selective assessment of the ‘uterine factor’. These authors also detected a 2-fold risk of miscarriage in women with adenomyosis. This suggests that the adenomyotic uterine environment increases the risk of miscarriage independently of oocyte and embryo quality. Also in this case heterogeneity was high, but the $I^2$ statistic was reduced at sensitivity analysis excluding the study by Salim et al. (2012) who reported a RR of 18.00 (95% CI, 4.08–79.47).

Live birth rate was reported in three studies, with an overall 30% reduction in the likelihood of delivering a viable baby. The combined estimate suggesting an association between adenomyosis and live birth is consistent with the findings of Martinez-Conejero et al. (2011), who reported a significant reduction of live birth rate per cycle in women with adenomyosis compared with those without the condition.

In general, the detrimental effect of adenomyosis on IVF/ICSI outcome appears to be related to both reduced probability of clinical pregnancy and increased risk of early pregnancy loss. There are various possible biological interpretations for this effect, including the chronic inflammatory condition caused by infiltration of endometrial glands in the myometrium (Tremellen and Russell, 2012), the increased local estrogen production due to aromatase P450 overexpression (Brosens et al., 2004), dysperistalsis resulting in impaired utero-tubal rapid sperm transport (Kissler et al., 2006), and alterations of adhesion molecules, cell proliferation, apoptosis, and free radical metabolism (Benagiano et al., 2012, 2013). If this is true, suppression of adenomyosis by long-term down-regulation with GnRH agonists might improve IVF/ICSI outcome. Indeed, in the two negative studies (Mijatovic et al., 2010; Costello et al., 2011) a long down-regulation protocol was used and heterogeneity was absent, whereas in all four studies in which a short GnRH agonist protocol was applied (Maubon et al., 2010; Youm et al., 2011; Salim et al., 2012; Thalluri and Tremellen, 2012), a major difference in clinical pregnancy rate was observed, although heterogeneity was moderate to high.

Also the potential effect of adenomyosis on implantation has been debated recently. Whereas Campo et al. (2012a,b) hypothesized a detrimental impact mediated by perturbed uterine peristalsis and reduced endometrial receptivity indicated by the presence of implantation marker defects, Martinez-Conejero et al. (2011) and Vila-Vives et al. (2012) reported no statistically significant differences in implantation and pregnancy rates between women with or without adenomyosis diagnosed at TVUS. However, if adenomyosis is considered a uterine factor of infertility, it seems logical to infer that impaired implantation constitutes the pathogenic mechanism leading to reduced clinical pregnancy rate.

Theoretically, MRI could have allowed better discrimination between the group of women with adenomyosis and that without adenomyosis. If this was true, findings of studies in which MRI was employed for diagnosis could be considered more reliable than those of studies in which TVUS was used, also taking into consideration that the accuracy of TVUS is more instrument- and operator dependant than that of MRI. In fact, disease misclassification in studies adopting TVUS could have led to inclusion of some women with minor forms of adenomyosis in the no

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**Table**

<table>
<thead>
<tr>
<th>Source</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>Adenomyosis Events</th>
<th>No-Adenomyosis Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chi et al.</td>
<td>1999</td>
<td>3.17 (1.37, 7.31)</td>
<td>4/10</td>
<td>9/38</td>
</tr>
<tr>
<td>Mijatovic et al.</td>
<td>2010</td>
<td>0.78 (0.33, 1.86)</td>
<td>4/11</td>
<td>14/30</td>
</tr>
<tr>
<td>Costello et al.</td>
<td>2011</td>
<td>0.57 (0.15, 2.17)</td>
<td>2/13</td>
<td>18/59</td>
</tr>
<tr>
<td>Martinez-Conejero et al.</td>
<td>2011</td>
<td>2.01 (1.29, 3.12)</td>
<td>43/131</td>
<td>24/147</td>
</tr>
<tr>
<td>Youm et al.</td>
<td>2011</td>
<td>2.46 (1.51, 4.01)</td>
<td>21/66</td>
<td>29/224</td>
</tr>
<tr>
<td>Salim et al.</td>
<td>2012</td>
<td>18.00 (4.08, 79.47)</td>
<td>2/4</td>
<td>3/108</td>
</tr>
<tr>
<td>Thalluri and Tremellen</td>
<td>2012</td>
<td>2.70 (0.31, 23.55)</td>
<td>1/10</td>
<td>3/61</td>
</tr>
<tr>
<td>Overall ($I^2$ = 67.7%, p = 0.005)</td>
<td></td>
<td>2.12 (1.20, 3.75)</td>
<td>77/241</td>
<td>97/687</td>
</tr>
</tbody>
</table>

**Figure 3** Forest plot showing individual and combined effect size estimates and 95% confidence intervals (CIs) in studies that evaluated the risk of miscarriage in clinical pregnancies obtained at IVF/ICSI in women with or without adenomyosis. Horizontal lines indicate 95% CIs; boxes show the study-specific weight; diamond represents combined effect size; dashed line indicates the overall estimate.
adenomyosis group, leading to underestimation of the association between adenomyosis and IVF/ICSI outcome. Heterogeneity was absent or low when studies were classified based on diagnostic modality. However, both studies in which MRI was used were also prospective (Maubon et al., 2010; Ballester et al., 2012). Therefore, it is also possible that greater attention to adenomyosis detection resulted in better discrimination between women with and without the condition independently of the diagnostic instrumentation adopted. Indeed, heterogeneity was low also when studies were stratified based on design. In prospective trials adenomyosis was associated with an overall halving of the likelihood of clinical pregnancy, whereas no statistically significant effect was found in retrospective ones after data pooling, although in this case the higher confidence limit was barely above unity. Actually, interactions between study design and diagnostic modality are difficult to disentangle.

More in general, when MRI was used, the diagnosis was based exclusively on the junctional zone thickness (the so-called ‘myosis’ component). On the other hand, when TVUS was used, the diagnostic criteria always included, besides junctional zone thickness anomalies, the presence of ‘aneoid’, ‘cystic’, ‘hypoechoic’, ‘poorly circumscribed’ areas within the myometrium (the so-called ‘adeno’ component). Moreover, in some studies diagnostic criteria differed even with regard to the same diagnostic modality. As an example, at MRI, Maubon et al. (2010) and Ballester et al. (2012) used a different cut-off junctional zone thickness. In particular, only the latter authors used the widely accepted limit of 12 mm. These differences in diagnostic criteria may have led to selection of different study groups, thus limiting between-study comparability.

There is ample evidence that endometriosis and adenomyosis may coexist. The proportion of women with both diseases remains controversial and differences have been attributed to variable MRI diagnostic criteria, i.e. whether a junctional zone cut-off thickness of 10 or 12 mm is chosen (Kunz et al., 2005; Bazot et al., 2006). Even taking available figures with caution, between one-fourth and one-third of the women enrolled in the selected studies might have had both conditions. Since endometriosis has been associated with subfertility and with reduced likelihood of conception after assisted reproductive technologies, it would have been interesting to define IVF outcome in women with adenomyosis only and in those with endometriosis in addition to adenomyosis. However, based on the analysis of the available evidence, it is difficult to understand to which extent IVF failure and early pregnancy complications were related to presence of endometriosis rather than presence of adenomyosis per se. In fact, the use of laparoscopy to confirm the diagnosis of endometriosis was inconsistent among studies, and the modality and extent of lesion treatment were often undefined. These variables may impact on the potential effect of endometriosis on IVF outcome. Moreover, it was not possible to extract separately the number of conceptions in the group of women with a diagnosis of endometriosis in addition to adenomyosis and in the group of women with adenomyosis only. The results of the two studies with the lowest prevalence of concomitant endometriosis (Salim et al., 2012;
Thalluri and Tremellen (2012) still demonstrated a greatly reduced likelihood of clinical pregnancy after IVF/ICSI in the adenomyosis group. Moreover, at meta-regression no association was observed between prevalence of endometriosis and likelihood of clinical pregnancy in the selected studies. These findings do not seem to support a large effect of endometriosis in addition to (or instead of) that of adenomyosis. However, endometriosis could have acted as a confounder anyway, and research is needed to disentangle this issue.

Despite exclusion of studies that had not been published in full in peer-reviewed journals, also qualitative heterogeneity among the selected studies was elevated, owing to differences in age of participants, duration of infertility, co-existence of additional pelvic disorders, type of down-regulation protocol used, quality, number, and stage of embryos transferred, number of IVF/ICSI cycles carried out, and the modality itself for the diagnosis of adenomyosis. More than half of the considered studies performed sub-optimally in terms of selection of participants, comparability of study groups or assessment of exposure. In particular, although the diagnostic criteria described were consistently indicative of inclusion of only severe adenomyosis forms, the variable prevalence of the condition in the infertile population undergoing IVF/ICSI suggests that this may not have been always the case. Even excluding the extreme estimates (Martínez-Conejero et al., 2011; Salim et al., 2012), percentages still varied from 11.7% (Chiang et al., 1999) to 28.0% (Ballester et al., 2012). Reasonably, if adenomyosis has an effect on IVF/ICSI outcome, more severe forms should be associated with a higher detrimental impact. However, no relation was observed between adenomyosis prevalence in individual studies and IVF/ICSI outcome. Finally, the large variation in sample size could have influenced the overall estimates, although funnel plot analysis never suggested small study effects. Eventually, even considering all the limitations inherent in the published reports, the data included in our analysis are the only available evidence on which to base clinical understanding and treatment decision-making.

The production of tight confidence intervals around spurious results is a danger inherent to meta-analyses involving observational studies. In fact, in these circumstances it is difficult to control for confounding and selection bias, and it would be better to put great efforts in assuring a complete literature search, in defining an objective and reproducible modality for study selection and data extraction, and in the meticulous examination of potential sources of heterogeneity among studies, instead of focusing on the statistical aspects of data pooling (Egger et al., 1998).

In this regard, a thorough literature review was performed and different strategies for article search were adopted with the aim of avoiding major bias in data gathering. Moreover, two independent observers extracted data from the included reports. We indicated the studies that were rejected and described the reasons for their exclusion. Heterogeneity was explored in funnel plots and at sensitivity analysis. Finally, potential sources of confounding and bias were addressed in detail (Egger et al., 1997).
Overall, assessment of secondary outcomes, as well as subgroup analyses, fit with an association between adenomyosis and IVF/ICSI outcome, thus strengthening the validity of the general result. In particular, confounding per se may hardly explain the large increase in risk of miscarriage observed in patients with the condition. Unfortunately, a dose–response effect could not be assessed, as in no study the severity of adenomyosis in terms of depth of penetration and extension of lesions was defined.

**Conclusions**

Adenomyosis appeared to have a detrimental impact on IVF/ICSI outcome in terms of reduction in clinical pregnancy rate and increase in miscarriage risk, although the potential confounding effect of endometriosis could not be adequately assessed. The decrease in the probability of achieving a viable pregnancy should be discussed with infertile women with a diagnosis of adenomyosis who are considering IVF/ICSI. On the other hand, patients should also be informed that actual estimates may reveal imprecise, and that the available information should be integrated with several other variables that may have an impact on the likelihood of success.

It seems reasonable to suggest screening for adenomyosis before embarking in medically assisted reproductive procedures. However, findings on the modality used for adenomyosis detection should be considered with caution due to the possibility of confounding. Therefore, although MRI may theoretically provide better information than TVUS, the latter approach should be preferred for screening purposes, given its ubiquitous availability and low cost, whereas MRI could be reserved for diagnosis in selected circumstances. Additional data are needed to clarify the effect of the duration of down-regulation on IVF outcome. Meanwhile, it seems prudent to adopt long-term protocols in women with adenomyosis.

In future studies on the association between adenomyosis and IVF/ICSI outcome, a case–control design should be adopted, with a pre-planned power calculation, and with matching for age, indicators of ovarian reserve, and presence of additional pelvic disorders. In particular, discrimination is needed between women with adenomyosis only and those with endometriosis in addition to adenomyosis. The diagnosis of adenomyosis should be standardized according to internationally agreed criteria, with the objective of selecting definite populations in terms of disease severity (Gordts et al., 2008). Crude numbers should be reported for all outcomes, with unequivocal definitions of numerators and denominators. Moreover, only the results regarding the first cycle should be considered, as this allows a more accurate estimate of the effect (Costello et al., 2011). Live birth should be the default primary outcome, as failure to report it constitutes a major source of bias (Clarke et al., 2010). In addition, more research is needed on the potential consequences of adenomyosis in terms of major obstetrical syndromes, such as spontaneous late miscarriage, preterm birth, intrauterine growth restriction, pre-eclampsia and obstetric haemorrhages (Brosens et al., 2010).
In this regard, it has been suggested that alterations in the inner myometrium of women with adenomyosis may result in defective remodelling of the spiral arteries from the onset of decidualization (Brosens et al., 2013). This would lead to vascular resistance and increased risk of defective deep placentaion. Therefore, fetal health should be carefully assessed and considered as a major outcome too.

Finally, the effect of new excisional techniques of adenomyotic lesions (Grimbizis et al., 2013) on IVF/ICSI outcome should be evaluated.

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

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Authors’ roles
Conception and design: P.V. Literature search and data extraction: D.D. and B.B. Assessment of quality of studies: M.P.F. and P.V. Analysis and interpretation of data: D.C., P.V. and E.S. Drafting the article: P.V. Critical revision of the article for intellectual content: all authors. All the authors approved the final version of the manuscript.

Conflict of interest
The authors declare that they have no conflicts of interest.

References


