SYMPOSIUM: REPRODUCTIVE SURGERY

REVIEW

Is another meta-analysis on the effects of intramural fibroids on reproductive outcomes needed?

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Abstract Intramural fibroids when encountered in women undergoing fertility treatment present a clinical dilemma. Despite recent studies that have suggested a negative outcome for intramural fibroids on fertility outcomes, the evidence remains far from conclusive. The current study presents a systematic review and meta-analysis of the currently available evidence. Relevant articles were identified in MEDLINE and EMBASE. Ten studies reported the effects of intramural fibroids on assisted conception treatment including one study reporting the effect of myomectomy for these fibroids. Combined analysis of the included studies, after taking into account possible confounding factors, showed no evidence of a significant effect for intramural fibroids on clinical pregnancy rate (odds ratio (OR) 0.74, 95% confidence intervals (CI) 0.50–1.09), live birth rate (OR 1.17, 95% CI 0.62–2.22) or miscarriage rate (OR 1.61, 95% CI 0.61–4.20). There was also no evidence for a significant effect for myomectomy on the clinical pregnancy rate (OR 1.88, 95% CI 0.57–6.14) or the miscarriage rate (OR 0.89, 95% CI 0.14–5.48). These findings highlight the current deficiency in the literature and suggest that evidence is insufficient to draw any conclusions regarding the effect of intramural fibroids on reproductive outcomes.

Introduction

The presence of fibroids is not an uncommon finding in women with reproductive problems. Whereas there is good evidence to support the presence of an adverse effect for submucous fibroids distorting the endometrial cavity on reproductive outcomes (Pritts et al., 2009), the case is not so for those in which intramural fibroids are diagnosed, where there is still much debate regarding the possible effects of these fibroids on reproductive outcomes.
surprisingly, there is considerable controversy on when intramural fibroids should be removed to improve reproductive outcomes.

Despite the large number of studies in the literature addressing the issue of fibroids on reproductive performance, only a few of these studies have addressed intramural fibroids as a separate entity. Even fewer studies have compared reproductive performance prior to and after myomectomy for intramural fibroids and many of these are cohort studies without controls (Farquhar, 2009).

There have been two recent meta-analyses (Pritts et al., 2009; Sunkara et al., 2010) that suggest that intramural fibroids may have an adverse effect on pregnancy and miscarriage rates. Despite the high quality of these studies, several methodological problems related to study selection and dealing with confounding factors may affect the quality of the evidence. The current systematic review aims to evaluate the evidence for the effects of solely intramural fibroids with no cavity distortion on fertility outcomes on natural and assisted conception. The role of study bias including study design and confounding factors are considered.

Materials and methods

A systematic review and meta-analysis of the role of intramural fibroids with no cavity distortion on fertility outcomes on natural and assisted conception was undertaken.

Criteria for study inclusion

All studies reporting on clinical pregnancy, live birth or miscarriage rates after natural or assisted conception in women with intramural fibroids were sought. Studies that investigated these outcomes before and after myomectomy for intramural fibroids were also included. The following inclusion criteria were used.

Intramural fibroids were analysed separately. As this study aimed to examine the effects of only intramural fibroids and to avoid potential bias that may be produced by the additional presence of subserous fibroids (non-cavity distorting fibroids), studies that stated that intramural fibroids were examined together with subserous fibroids were not included. Studies that clearly stated that intramural fibroids were being examined were included. Where studies stated that intramural fibroids with a subserous component were being examined, the study was included only if the maximum fibroid diameter was 5 cm or less and the subserous component was less than 50%.

Submucous fibroids had been excluded by objective examination of the endometrial cavity by methods including hysteroscopy, hysteroscopy, ultrasonography and sonohysterography.

A comparison group was present. Where studies examined reproductive outcomes in women with fibroids conceiving naturally or with assisted conception, the control group was a group of women without fibroids and conceiving in a similar manner. Where the study examined the effect of myomectomy, the control group was either a group of women not undergoing myomectomy or the same cohort acting as their own controls (pre-myomectomy versus post-myomectomy). Descriptive cohort studies that did not include controls were therefore excluded.

Participants

Participants included women suffering from intramural fibroids attempting to conceive naturally, with assisted methods (IVF, intracytoplasmic sperm injection (ICSI) or embryo replacement) or after myomectomy (laparoscopic or open myomectomy).

Outcome measures

Primary

For the live birth rate (LBR), only studies that reported the LBR alone without the ongoing clinical pregnancy rate (CPR) were included in the analysis of this outcome.

Secondary

CPR was defined as the visualization of a healthy gestational sac and or a fetal echo with positive heart rate pulsations noted by ultrasound scan in the first trimester.

Miscarriage rate (MR) as defined by the rate of pregnancy loss before 20 weeks of gestation.

Search strategy

This study conducted a systematic search for all relevant articles in MEDLINE from 1964 to May 2010 and EMBASE from January 1980 to May 2010, using a combination of the following search terms; fibroid/fibroids, leiomyoma/leiomyomas, miscarriage/abortion/pregnancy, IVF/ICSI, myomectomy. Articles related to those retrieved using these search terms were also searched to ensure no relevant articles were missed (Figure 1). No restrictions were placed on language.

Data extraction

All relevant studies were included regardless of whether prospective or retrospective. For each trial, information was collected regarding the study design, the population size, inclusion and exclusion criteria, type of surgery, surgical complications maximum number and size of fibroids, LBR, CPR and MR.

Quality of included studies

The following items were considered for quality assessment: (i) a prospective design was used; (ii) the sample size was based on a power calculation; (iii) an intrauterine component was excluded using hysteroscopy or sonohysterography; (iv) age was not a confounding factor where either older-aged patients (>40 years old) had not been included, there was no significant age difference between the study and control groups or a statistical method such as multivariate analysis had been performed to account for any differences; (v) other relevant uterine abnormalities such as uterine septae had been excluded; and (vi) subserous fibroids were not a significant part of the analysis as explained...
above. Based on these criteria, the quality of the studies included in the meta-analysis can be seen in Table 1.

**Risk of bias assessment**

For assessment of risk of bias, the Newcastle–Ottawa scale for assessment of case–control studies was used, based on the recommendation of the Cochrane Collaboration (Higgins and Green, 2008; Wells et al., 2008). The system employs a star rating system for assessment of three main areas, selection, comparability and exposure. The maximum number of stars that can be awarded in these areas is four, two and three, respectively. Although there is no cut-off limit as yet to classify studies into ‘good’ or ‘bad’ based on this score, a cut-off limit of five stars has been used to identify studies with a low risk of bias (Aziz et al., 2006; Millett et al., 2008). This is based on the assumption of equal weight for the different parameters included in the scale. However, this particular study considered that accounting for confounding factors, particularly age and having a normal endometrial cavity, were amongst the most important factors that ensure comparability of cases and controls. We therefore used a cut off of five provided that the study scored at least one star in the comparability category.

Only one randomized controlled trial (RCT) was identified (Casini et al., 2006) and risk of bias assessment showed that, despite its randomized design and the exclusion of cavity involvement, there were several reasons to suspect significant bias. Firstly a power calculation had not been performed and secondly there was no indication that allocation had been concealed. Results of the risk of bias assessment for the case–control studies can be seen in Table 2.

**Quantitative data analysis**

Dichotomous data were extracted from the individual studies and expressed as combined odds ratio (OR) with 95% confidence intervals (CI) and then combined for meta-analysis.
with the RevMan software (Review Manager, 5.0.21; The Nordic Cochrane Centre, Copenhagen, The Cochrane Collaboration, 2009). Statistical heterogeneity was determined by examining the results of the chi-squared and $I^2$ statistics. A chi-squared statistic that was larger than its degree of freedom or an $I^2$ statistic with a value greater than 50%, provided evidence for significant heterogeneity between studies. Where there was evidence for statistical heterogeneity, a random effect model was used for meta-analysis; otherwise a fixed effect model was used.

Separate analysis was performed for the following: (i) the impact on the presence of intramural fibroids on reproductive outcomes for patients conceiving naturally; (ii) the impact on the presence of intramural fibroids on reproductive outcomes for patients conceiving with assisted conception treatment; and (iii) the impact of myomectomy.

In order to consider the impact of the risk of bias for individual studies and for important confounders, particularly age and screening procedures to exclude endometrial cavity involvement, sensitivity analyses were undertaken as follows.

Firstly, an analysis was performed of studies with a low risk of bias that included studies scoring five stars or more (including at least one star for the comparability category) on the Newcastle–Ottawa scale. Secondly, an analysis was performed of studies with a low risk of bias that included studies scoring five stars or more (including at least one star for the comparability category) on the Newcastle–Ottawa scale.

Secondly, an analysis was performed of studies with age did not appear to be a significant confounding factor. These were defined as studies where the examined cohort was less than 40 years of age and there was no significant age difference between the groups. This resulted in two studies being excluded because cases and controls were ≥40. Although these studies included embryo transfer cycles using donated embryos, there were no data regarding the age of the donors and whether or not there was any difference in the age of those donating to cases and those donating to controls (Dietterich et al., 2000; Horcajadas et al., 2008). Three other studies were excluded because there was a significant difference in age between the study and control groups (Hart et al., 2001; Khalaf et al., 2006; Klatsky et al., 2007).

Thirdly, an analysis was performed of studies where hysteroscopy or sonohysterography was used to exclude cavity involvement as this is considered superior to conventional transvaginal 2D ultrasound.

Finally, a combination of the second and third analyses was performed.

### Results

#### Details of retrieved studies

Thirty-six studies were retrieved for further evaluation. Twenty-six studies were then excluded for the following reasons: (i) grouping together of subserous and intramural fibroids (Check et al., 2002; Eldar-Geva et al., 1998; Farhi et al., 1995; Gavai et al., 2007; Li et al., 1999; Marchionni et al., 2004; Ramzy et al., 1998; Stovall et al., 1998; Wang and Check, 2004; Yarali and Bukulmez, 2002); (ii) studies with designs that were not directly relevant to the current clinical question (Benson et al., 2001; Bernard et al., 2000; Bulletti et al., 2004; Darai et al., 1997; Exacoustos and Rosati, 1993; Feinberg et al., 2006; Ng and Ho, 2002; Seoud et al., 1992; Sinclair et al., 2005; Sudik et al., 1996; Wang et al., 2001); (iii) the absence of an appropriate control group (Campo et al., 2003; Jun et al., 2001; Oliveira et al., 2004); and (iv) inclusion of submucous fibroids (Gianaroli et al., 2005; Surrey et al., 2005).

#### Included studies

### Study design

Ten studies were included in the final analysis, of which only one was a RCT of myomectomy (Casini et al., 2006), two were prospective comparative analyses (Hart et al., 2001; Ng et al., 2005) and the remaining were retrospective (Table 3).

#### Participants

Nine studies examined fertility outcomes in infertile women undergoing assisted reproductive treatments including IVF/ICSI/embryo transfer and only one study provided data for fertility outcomes in women conceiving naturally after

<table>
<thead>
<tr>
<th>Study</th>
<th>Selection</th>
<th>Comparability</th>
<th>Exposure</th>
<th>Total star score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bozdag et al. (2009)</td>
<td>****</td>
<td>*</td>
<td>***</td>
<td>9</td>
</tr>
<tr>
<td>Dietterich et al. (2000)</td>
<td>****</td>
<td>1</td>
<td>***</td>
<td>7</td>
</tr>
<tr>
<td>Hart et al. (2001)</td>
<td>****</td>
<td>*</td>
<td>***</td>
<td>8</td>
</tr>
<tr>
<td>Horcajadas et al. (2008)</td>
<td>**</td>
<td>*</td>
<td>***</td>
<td>6</td>
</tr>
<tr>
<td>Khalaf et al. (2006)</td>
<td>****</td>
<td>*</td>
<td>***</td>
<td>8</td>
</tr>
<tr>
<td>Klatsky et al. (2007)</td>
<td>**</td>
<td>1</td>
<td>***</td>
<td>5</td>
</tr>
<tr>
<td>Ng et al. (2005)</td>
<td>****</td>
<td>*</td>
<td>***</td>
<td>8</td>
</tr>
<tr>
<td>Surrey et al. (2001)</td>
<td>****</td>
<td>*</td>
<td>***</td>
<td>9</td>
</tr>
<tr>
<td>Vimercati et al. (2007)</td>
<td>****</td>
<td>*</td>
<td>***</td>
<td>9</td>
</tr>
</tbody>
</table>
Table 3  Characteristics of included studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Surgical complications</th>
<th>Population characteristics</th>
<th>Maximum fibroid size (cm)</th>
<th>Maximum fibroid number</th>
<th>Outcomes analysed by ICS</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Relevant outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bozdag et al. (2009)</td>
<td>Retrospective case–control analysis</td>
<td>No</td>
<td>61 patients with IM fibroids and 444 controls. All patients suffered from severe male factor infertility necessitating ICSI treatment</td>
<td>4.3</td>
<td>1</td>
<td>No No No</td>
<td>Exclusion criteria not fulfilled</td>
<td>(i) Endocervical or intrauterine pathology; (ii) previous uterine surgery; (iii) &gt;1 fibroid</td>
<td></td>
</tr>
<tr>
<td>Casini et al. (2006)</td>
<td>Prospective, RCT, surgical study comparing myomectomy to conservative treatment</td>
<td>Yes Not discussed</td>
<td>45 infertile women</td>
<td>5</td>
<td>Not stated</td>
<td>No No No</td>
<td>(i) Age &lt;35 years; (ii) one fibroid &lt;40 mm size; (iii) no other causes of infertility</td>
<td>(i) ≥2 fibroids; (ii) BMI &gt;20% overweight; (iii) recent use of steroid hormonal therapy</td>
<td></td>
</tr>
<tr>
<td>Dietterich et al. (2000)</td>
<td>Retrospective case–control analysis</td>
<td>No</td>
<td>9 patients with IM fibroids and 11 controls</td>
<td>2.6</td>
<td>6</td>
<td>No No No</td>
<td>(i) First cycle of embryo transfer; (ii) &gt;35 years old</td>
<td><em>CPR</em></td>
<td></td>
</tr>
<tr>
<td>Hart et al. (2001)</td>
<td>Prospective analysis</td>
<td>No</td>
<td>112 patients with IM fibroids and 322 controls undergoing their first IVF/ICSI cycle</td>
<td>5</td>
<td>4</td>
<td>No No No</td>
<td>Fibroids ≤5 cm</td>
<td>(i) Previous myomectomy or uterine surgery; (ii) uterine cavity anomalies</td>
<td><em>CPR</em></td>
</tr>
<tr>
<td>Horcajadas et al. (2008)</td>
<td>Retrospective case–control analysis</td>
<td>Yes Not discussed</td>
<td>807 donor oocyte recipients</td>
<td>Not stated (&gt;5)</td>
<td>Not stated (&gt;3)</td>
<td>Yes Yes No</td>
<td>First cycle of treatment</td>
<td>(i) Donor oocyte treatment; (ii) cryopreserved embryo transfers</td>
<td></td>
</tr>
<tr>
<td>Khalaf et al. (2006)</td>
<td>Retrospective analysis</td>
<td>No</td>
<td>First three IVF/ICSI cycles over 1-year period for 112 patients with IM fibroids and 322 controls</td>
<td>5</td>
<td>4</td>
<td>No No No</td>
<td>Fibroids ≤5 cm</td>
<td>(i) Concomitant adenomyosis or endometriosis; (ii) previous uterine surgery; (iii) severe male factor infertility</td>
<td><em>CPR</em></td>
</tr>
</tbody>
</table>

(Table 3 continued on next page)
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Surgical study$^a$</th>
<th>Surgical complications</th>
<th>Population characteristics</th>
<th>Maximum fibroid size (cm)</th>
<th>Maximum fibroid number</th>
<th>Outcomes analysed by Inclusion criteria</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Relevant outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klatsky et al. (2007)</td>
<td>Retrospective cohort study</td>
<td>No</td>
<td>NA</td>
<td>369 donor oocyte recipients</td>
<td>Not stated (&gt;4)</td>
<td>Not stated</td>
<td>Yes Yes No</td>
<td>(i) First cycle of treatment; (ii) only fresh cycles</td>
<td>(i) Missing data regarding age and number of embryo received; (ii) patients with adenomyosis; (iii) patients with Müllerian abnormalities; (iv) patients with cancelled cycles</td>
<td>CPR, MR</td>
</tr>
<tr>
<td>Ng et al. (2005)</td>
<td>Prospective</td>
<td>No</td>
<td>NA</td>
<td>50 patients with IM fibroids and 50 controls undergoing IVF/ET</td>
<td>Not stated</td>
<td>Not stated</td>
<td>No No No</td>
<td>(i) Non-smokers; (ii) oestradiol &lt; 20 000 mIU/ml on the day of HCG</td>
<td>(i) Previous myomectomy; (ii) endometrial lining not clearly visualized</td>
<td>CPR, MR</td>
</tr>
<tr>
<td>Surrey et al. (2001)</td>
<td>Retrospective case–control analysis</td>
<td>No</td>
<td>NA</td>
<td>399 consecutive IVF/ET cycles</td>
<td>3.6</td>
<td>Not stated</td>
<td>No No No</td>
<td>(i) The use of only autologous oocytes; (ii) day-3 FSH &lt; 10 mIU/ml and oestradiol &lt; 80 pg/ml; (ii) only fresh IVF/ET cycles</td>
<td>Inclusion criteria not fulfilled</td>
<td>CPR, LBR</td>
</tr>
<tr>
<td>Vimercati et al. (2007)</td>
<td>Retrospective case–control analysis</td>
<td>Yes</td>
<td>Not discussed</td>
<td>31 treatment cycles for patients with IM fibroids and 215 cycles for controls</td>
<td>Not stated</td>
<td>Not stated</td>
<td>No Yes No</td>
<td>All IVF/ICSI cycles in a 4-year period</td>
<td>Not specifically stated</td>
<td>CPR, MR</td>
</tr>
</tbody>
</table>

$^a$ Surgical study: denotes either a study that was primarily surgical (i.e., examining the effect of myomectomy) or a study that contained a surgical analysis as one of its components. CPR = clinical pregnancy rate; ET = embryo transfer; HCG = human chorionic gonadotrophin; ICSI = intracytoplasmic sperm injection; IM = intramural; LBR = live birth rate; MR = miscarriage rate; NA = not applicable; RCT = randomized controlled trial.
myomectomy (Casini et al., 2006). The maximum number of fibroids was clearly stated in six studies (Bozdag et al., 2009; Casini et al., 2006; Dietterich et al., 2000; Hart et al., 2001; Khalaf et al., 2006; Surrey et al., 2005) while in four studies no maximum number was stated (Horcajadas et al., 2008; Klatsky et al., 2007; Ng et al., 2005; Vimercati et al., 2007). Furthermore, one study limited the analysis to only single intramural fibroids (Bozdag et al., 2009).

Similarly, in six studies, the maximum size of the fibroids was not stated (Casini et al., 2006; Horcajadas et al., 2008; Klatsky et al., 2007; Ng et al., 2005; Surrey et al., 2005; Vimercati et al., 2007) while the remaining studies reported the size as ranging from 6 mm to 2.6 cm (Dietterich et al., 2000), from 5 mm to 43 mm (Bozdag et al., 2009) or as simply as ≤5 cm (Hart et al., 2001; Khalaf et al., 2006). Furthermore, only three studies attempted to take into consideration the size, location or number of the fibroids when analysing the outcomes (Horcajadas et al., 2008; Klatsky et al., 2007; Vimercati et al., 2007).

Interventions
One RCT (Casini et al., 2006) reported on the effect of myomectomy. The remaining studies considered the effect of intramural fibroids on fertility outcomes following fertility treatments.

Results of analysis

Natural conception

Only one study reported on pregnancy outcomes in women conceiving naturally after myomectomy versus a control group and found no evidence for a significant difference in the CPR between the groups (OR 1.90, 95% CI 0.60–6.10) or the MR (OR 0.90, 95% CI 0.14–5.50) (Casini et al., 2006).

In women/couples undergoing assisted reproductive treatment

For the analysis of LBR, a pooled analysis was performed of three studies including a total of 173 patients/cycles with intramural fibroids and 478 patients/cycles with no fibroids (Dietterich et al., 2000; Khalaf et al., 2006; Surrey et al., 2001). The analysis found no evidence of a significant difference in LBR between the groups (OR 0.95, 95% CI 0.47–1.92). There was evidence of significant heterogeneity amongst the included studies (chi-squared = 4.15, df = 2, P = 0.13, I² = 52%; Figure 2).

For the analysis of CPR, a pooled analysis was performed of nine studies with a total of 1300 patients/cycles with intramural fibroids and 1875 patients/cycles with no fibroids (Bozdag et al., 2009; Dietterich et al., 2000; Hart et al., 2001; Horcajadas et al., 2008; Khalaf et al., 2006; Klatsky et al., 2007; Ng et al., 2005; Surrey et al., 2001; Vimercati et al., 2007). The analysis found a significantly lower CPR in the women with intramural fibroids (OR 0.60, 95% CI 0.42–0.87) compared with women with no intramural fibroids. There was evidence of significant heterogeneity amongst the included studies (chi-squared = 20.67, df = 8, P = 0.008, I² = 61%; Figure 3).

For the analysis of MR, a pooled analysis was performed of four studies with 495 patients/cycles with intramural fibroids and 514 patients/cycles with no fibroids (Bozdag et al., 2009; Horcajadas et al., 2008; Ng et al., 2005; Vimercati et al., 2007). The analysis showed no evidence of a significant difference in the MR between the groups (OR 0.90, 95% CI 0.60–1.36).
There was no evidence for significant statistical heterogeneity between the studies (chi-squared = 2.60, df = 3, P = 0.46, I² = 0%; Figure 4).

Effect of myomectomy

Only one study examined this outcome (Casini et al., 2006).

For the analysis of LBR, no studies provided data for the LBR after myomectomy.

For the analysis of CPR, 23 post-myomectomy patients and 22 patients with no myomectomy were analysed for this particular outcome. There was no evidence for a significant effect for myomectomy on the CPR (OR 1.88, 95% CI 0.57–6.14).

For the analysis of MR, 13 post-myomectomy patients and 9 patients with no myomectomy were analysed for this particular outcome. There was no evidence for a significant effect for myomectomy on the MR (OR 0.89, 95% CI 0.14–5.48).

Sensitivity analysis: studies with a low risk of bias

For the analysis of LBR, a pooled analysis was performed of two studies (Khalaf et al., 2006; Surrey et al., 2001) including 163 patients/cycles with intramural fibroids and 466 patients/cycles. The analysis showed no evidence of a significant effect of fibroids on the LBR (OR 0.83, 95% CI 0.44–1.57). There was evidence for significant heterogeneity between studies (chi-squared = 2.24, df = 1, P = 0.13, I² = 55%).

For the analysis of CPR, a pooled analysis was performed of six studies (Bozdag et al., 2009; Horcajadas et al., 2008; Khalaf et al., 2006; Ng et al., 2005; Surrey et al., 2001; Vimercati et al., 2007) including 1110 patients/cycles with intramural fibroids and 1267 patients/cycles with no fibroids. The analysis showed a significant negative effect for intramural fibroids on the CPR between the groups (OR 0.76, 95% CI 0.61–0.96). There was no evidence of heterogeneity between studies (chi-squared = 4.77, df = 5, P = 0.44, I² = 0%; Figure 5).

For the analysis of MR, a pooled analysis was performed of four studies (Bozdag et al., 2009; Horcajadas et al., 2008; Ng et al., 2005; Vimercati et al., 2007) including 495 patients/cycles with intramural fibroids and 514 patients/cycles with no fibroids. There was no evidence for a significant difference in the MR between the groups (OR 1.60, 95% CI 0.96–2.68). There was no evidence of heterogeneity between studies (chi-squared = 2.60, df = 3, P = 0.46, I² = 1%).

Sensitivity analysis: studies where age was not a significant confounding factor

For the analysis of LBR, only one study remained that analysed this outcome (Surrey et al., 2001). There was no evidence of a significant effect of fibroids on the LBR (OR 0.17, 95% CI 0.62–2.22).

For the analysis of CPR, a pooled analysis was performed of four studies (Bozdag et al., 2009; Ng et al., 2005; Surrey et al., 2001; Vimercati et al., 2007) including 191 patients/cycles with intramural fibroids and 810 patients/cycles with no fibroids. There was no evidence of a significant difference in the CPR between the groups (OR 0.82, 95% CI 0.57–1.18). There was no evidence of significant heterogeneity between studies (chi-squared = 4.11, df = 3, P = 0.25, I² = 27%).

For the analysis of MR, a pooled analysis was performed of three studies (Bozdag et al., 2009; Ng et al., 2005; Vimercati et al., 2007) including 64 patients/cycles with intramural fibroids and 112 patients/cycles with no fibroids. The analysis showed no evidence of a significant effect for intramural fibroids on the MR between the groups (OR 1.60, 95% CI 0.96–2.68). There was no evidence of heterogeneity between studies (chi-squared = 2.60, df = 3, P = 0.46, I² = 0%).

Figure 4 The effect of presence of intramural fibroids on the miscarriage rate after assisted conception.

Figure 5 The effect of presence of intramural fibroids on the clinical pregnancy rate after assisted conception for studies with a low risk of bias.
intramural fibroids and 379 patients/cycles with no fibroids. There was no evidence of a significant difference in the MR between the groups (OR 1.16, 95% CI 0.48–2.82). There was no evidence of significant heterogeneity between studies (chi-squared = 2.02, df = 2, \( P = 0.36, I^2 = 1\%\)).

**Sensitivity analysis: studies that used a high-quality method (hysteroscopy or sonohysterography) exclude cavity involvement**

For the analysis of LBR, a pooled analysis was performed of two studies including 163 patients/cycles with intramural fibroids and 466 patients/cycles with no fibroids. The analysis showed no evidence of a significant difference in the LBR between the groups (OR 0.83, 95% CI 0.44–1.57) (Khalaf et al., 2006; Surrey et al., 2001). There was evidence of significant heterogeneity between studies (chi-squared = 2.24, df = 1, \( P = 0.13, I^2 = 95\%\)).

For the analysis of CPR, a pooled analysis was performed of six studies including 1174 patients/cycles with intramural fibroids and 1635 patients/cycles with no fibroids. The analysis showed evidence of a significant decrease in the CPR in the fibroid group (OR 0.60, 95% CI 0.39–0.91) (Bozdag et al., 2009; Hart et al., 2001; Horcajadas et al., 2008; Khalaf et al., 2006; Surrey et al., 2001; Vimercati et al., 2007). There was also evidence of significant heterogeneity between studies (chi-squared = 16.31, df = 5, \( P = 0.006, I^2 = 69\%\)).

For the analysis of MR, a pooled analysis was performed of three studies including 484 patients/cycles with intramural fibroids and 502 patients/cycles with no fibroids (Bozdag et al., 2009; Horcajadas et al., 2008; Vimercati et al., 2007). The analysis showed no evidence of a significant difference in the MR between the groups (OR 1.16, 95% CI 0.71–1.89). There was no evidence of heterogeneity between the included studies (chi-squared = 0.57, df = 2, \( P = 0.75, I^2 = 0\%\)).

**Sensitivity analysis: studies where both age and a likely confounding factor and a high-quality method was used to exclude cavity involvement**

For the analysis of LBR, only one study including 51 patients/cycles with intramural fibroids and 144 and 51 patients/cycles with no fibroids reported on the LBR (Surrey et al., 2001). The analysis showed no evidence of a significant difference in the LBR between the groups (OR 1.17, 95% CI 0.62–2.22).

For the analysis of CPR, a pooled analysis was performed of three studies (Bozdag et al., 2009; Surrey et al., 2001; Vimercati et al., 2007) including 143 patients/cycles with intramural fibroids and 763 patients/cycles with no fibroids, showing no evidence of a significant difference in the CPR between the groups (OR 0.74, 95% CI 0.50–1.09). There was no evidence of heterogeneity between the included studies (chi-squared = 2.08, df = 2, \( P = 0.35, I^2 = 4\%\)).

For the analysis of MR, a pooled analysis was performed of two studies (Bozdag et al., 2009; Vimercati et al., 2007) including 53 fibroid patients/cycles and 372 patients/cycles with no fibroids showed no evidence of a significant difference in the MR between the groups (OR 1.61, 95% CI 0.61–4.20). There was also no evidence of heterogeneity between the included studies (chi-squared = 0.02, df = 1, \( P = 0.88, I^2 = 0\%\)).

**Discussion**

Intramural fibroids remain an important clinical problem commonly encountered in patients with fertility problems and during the process of assisted conception. The question of whether these fibroids may impair reproductive performance and therefore need to be removed to improve fertility remains a matter of ongoing debate.

The current study has found that there is limited evidence to guide clinical decision-making in women with intramural fibroids who are infertile. Initial results suggest a negative impact for intramural fibroids on the CPR but not the LBR or MR. However, when the analysis is limited to only the highest quality studies then there was no longer evidence of a significant effect on the CPR. Findings pertaining to MR were the most consistent of all outcomes where the findings did not change after performing the sensitivity analysis and there was no evidence of statistical heterogeneity between the included studies. Nevertheless after accounting for age and cavity involvement, only two studies remained (Bozdag et al., 2009; Vimercati et al., 2007), indicating that until further well-designed studies are available, these findings should still be viewed with caution.

These findings are different to those of the two recent meta-analyses (Pritts et al., 2009; Sunkara et al., 2010) that have both suggested a negative influence for intramural fibroids on reproductive performance. This discrepancy in findings can be explained by several factors.

First and foremost is the way in which potential confounding factors were analysed. The most important confounding factors that need to be considered when examining this particular issue include age and the absolute absence of any cavity involvement as confirmed by high-quality diagnostic methods, such as sonohysterography and hysteroscopy, which have a higher sensitivity and specificity than hysteroscopy and conventional 2D ultrasonography (Cepni et al., 2005; de Vries et al., 2000; Karageyim Karsidag et al., 2010; Soares et al., 2000).

Recognizing the importance of these confounding factors, the meta-analysis of Pritts et al. (2009) performed a subgroup analysis including only studies that used highly accurate methods to exclude cavity involvement and found a significant adverse effect on the implantation rate but not on the CPR, LBR or the MR. The current study, when performing a similar subgroup analysis, found there was still a significant effect on the CPR; however, the upper limit of the confidence interval fell just short of the line of unity (95% CI, 0.39–0.91) and there was evidence of significant statistical heterogeneity between the included studies, thus casting doubts on the clinical significance of this finding.

Alternatively, the second meta-analysis (Sunkara et al., 2010) performed a subgroup analysis for studies that only included patients less than 37 years of age in order to minimize the confounding effect of age and found a significant reduction in the LBR. This is contrary to the findings of the current study when a similar subgroup analysis was performed, where no evidence of a significant effect was found on the CPR, LBR or MR.

Significant heterogeneity seems to be a persistent pattern in most studies and therefore casts doubts regarding the findings. To examine and account for this heterogene-
ity, a sensitivity analysis was performed including only studies that had a low risk of bias as determined by the Newcastle–Ottawa scale and for studies that accounted for both age and cavity involvement. Incidentally, the three studies that accounted for both these factors were also the highest scoring studies on the Newcastle–Ottawa scale (Bozdag et al., 2009; Surrey et al., 2001; Vimercati et al., 2007). By combining these two variables to include only the least biased studies, both clinical and statistical heterogeneity were minimized as shown by the I² statistic for CPR dropping from 61% to 0% for the least biased studies. When only the least biased studies that also accounted for age and excluded cavity involvement were examined, there was no longer any evidence of a significant negative impact on the CPR. Furthermore only one study remained for the analysis of LBR (Surrey et al., 2001), and again showed no evidence of a significant impact.

The current study used different selection criteria for inclusion of studies. Most primary studies that have addressed this issue group intramural fibroids with subserous fibroids as a single entity. This was also the approach taken by the two recent meta-analyses of Pritts et al. (2009) and Sunkara et al. (2010). The classification of fibroids into those encroaching on the endometrial cavity (i.e. submucous) and those not encroaching on the cavity (intramural and subserous), when analysing fertility outcomes, is based on the assumption that poor reproductive performance in women with fibroids occurs mainly when there is a space occupying lesion such as the case with submucous fibroids. However, there may be other explanations for poor reproductive performance associated with fibroids such as changes in endometrial blood flow, uterine contractility or the release of inflammatory substances (Donnez and Jadoul, 2002).

One particular study examining the relationship between the uterine vascular patterns of non-cavity distorting fibroids and reproductive outcomes during controlled ovarian stimulation, found that patients who successfully conceived had lower uterine artery vascular resistance and that a preferential blood flow towards the fibroids with a resulting decreased endometrial blood flow could be associated with a lower pregnancy rate (Ng and Ho, 2002).

Although the same group later explored this hypothesis further by specifically examining endometrial blood flow in women with intramural fibroids and found no significant effect (Ng et al., 2005), it is still plausible that the inclusion of large or numerous subserous fibroids may influence the effects of intramural fibroids. A homogenous group of patients with only intramural fibroids would therefore provide the best population to answer the current clinical question.

Accordingly, the current study included only patients with intramural fibroids and where subserous fibroids, if present, were not judged to be a significant confounding factor in the analysis. Nevertheless, this was difficult since a clear definition of intramural fibroids was often lacking in the primary studies. These different inclusion criteria partially explain the difference in included studies in the current analysis compared with that by Pritts et al. (2009). In the current study, an additional six studies were included (Bozdag et al., 2009; Horcajadas et al., 2008; Khalaf et al., 2006; Ng et al., 2005; Surrey et al., 2001; Vimercati et al., 2007) and several were excluded for reasons stated above. It is interesting that the analysis by Pritts et al. (2009) did not include the study by Khalaf et al. (2006) but included the study by Hart et al. (2001). It may be argued that both studies included similar populations and therefore only one of then need to be included. The current study included both, since the study by Khalaf et al. (2006) examined cumulative pregnancy rates whilst the earlier study by Hart et al. (2001) only examined the first IVF cycle outcome. In summary, future studies need to focus on the careful description and inclusion of intramural fibroids not associated with a subserous component to minimize the risk of bias.

Regarding future studies, several findings from the current study need to be taken into consideration. Firstly, studies should consider the number, site and size of the fibroids when analysing their outcomes. Only three studies performed some form of subgroup analysis for outcomes in view of the size, number of fibroids (Horcajadas et al., 2008; Klatsky et al., 2007; Vimercati et al., 2007) but the method used was non-consistent across these studies and therefore did not allow for a meta-analysis of the combined results. However a dose-dependent relationship between fertility outcomes and the number of fibroids has been demonstrated in at least one study (Check et al., 2002). Although this study was excluded from the meta-analysis due to the inclusion of subserous fibroids, other aspects of its design are of particular interest. It is the only study to have analysed the outcomes by both number and location of the fibroids. By including a detailed subclassification of the number of fibroids from one to seven, this study reported a progressive drop in the CPR with an increasing number of fibroids. Future studies should follow this example since it would allow a detailed analysis of the outcomes based on different cut-off limits for number of fibroids. A similar design should also be adopted when reporting on the fibroid size, since no single study so far has provided us with the answer as to the cut-off size at which intramural fibroids may adversely affect fertility outcomes and hence may need to be removed. One possible way to combine site, size and location would be to calculate the total volume of fibroids within the myometrium at a specific location and report the outcomes using different cut off limits for fibroid volume. This would be difficult to achieve except in well-designed multicentre prospective studies in order to achieve the required sample size and hence have adequate power.

Secondly, other important confounding factors need to be taken into consideration in future analyses such as body mass index and smoking. Both of these have been shown to negatively affect fertility outcomes (Fedorcsak et al., 2004; Metwally et al., 2008; Waylen et al., 2009). Few studies have accounted for these variables in their analyses, including the studies by Horcajadas et al. (2008), Casini et al. (2006) and Ng et al. (2005) where clearly no obese patients had been included. Similarly non-smokers were excluded from the analysis in only one study (Ng et al., 2005).

Another confounding factor is that of the cause of infertility, where mixing patients with different causes of infertility may introduce bias. This issue was addressed in one particular study where only patients with a single cause of infertility (severe male factor) were included (Bozdag
et al., 2009). Probably the best cohort that may be used to address the question at hand would be that with unexplained infertility, but again adequate numbers may be difficult to achieve in any single-centre study since fibroids are diagnosed as the only cause for infertility in less than 3% of cases (Farquhar, 2009).

Thirdly, another problem was that most studies report the LBR combined with the ongoing CPR. Ideally in any study regarding fertility outcomes, the LBR alone should be the main outcome of interest, since this outcome is the one most relevant to the patient. Substituting missing data for LBR by using the ongoing CPR may introduce bias by not accounting for late fetal loss, especially as fibroids are recognized to cause an increase in mid-trimester loss and preterm labour (Chen et al., 2009). Future studies should therefore endeavour to report only the LBR.

Fourthly, and although the current study aimed to provide information related to the effect of presence of intramural fibroids on reproductive outcomes based on the method of conception (natural versus assisted conception), the majority of the evidence pertains to those undergoing assisted conception. There are no studies that examine the effect of untreated fibroids on natural conception and only one study that has examined the effect of myomectomy on natural conception (Casini et al., 2006). There is therefore a need for studies that examine outcomes in a cohort of patients with intramural fibroids attempting natural conception with no intervention to assist conception or remove the fibroids.

Finally and in agreement with the study by Pritts et al. (2009), the current study emphasizes the fact that there are not enough studies regarding the effect of removal of intramural fibroids on reproductive outcomes. Since complications of surgery may outweigh any benefits, this issue needs to be addressed in large randomized controlled trials with adequate sample size before any conclusion can be drawn; so far the question has been addressed in only one study which did not show benefit (Casini et al., 2006). However for such a trial to be ethically justified, a clear adverse effect for intramural fibroids must be unequivocally demonstrated, if it indeed exists. Therefore, studies addressing the adverse effect of reproductive outcome should currently take precedence over interventional studies.

Furthermore with the increasing use of the laparoscopic myomectomy in women with fertility problems, possibly in a belief that this may be associated with a benefit to reproductive outcomes, there is a desperate need that future studies address laparoscopic myomectomy as a separate surgical intervention. A large multicentre prospective study could be the best way to ensure an adequate sample size in order to answer this question in the near future.

Before concluding, it must be recognized that having more strict criteria for study inclusion in this current analysis has led to inclusion of fewer studies, which may have led to a loss of statistical power. However this only serves to further highlight the need for more high-quality studies.

In conclusion, the main contribution of this study is not by providing a definitive answer to the question of intramural fibroids and reproductive performance but rather by highlighting the deficiency that exists in the current literature. Contrary to the findings of the two previous meta-analyses, this study suggests that there is in fact insufficient evidence to draw any conclusions regarding the effect of intramural fibroids on reproductive outcomes. Despite the importance of meta-analyses in bringing together and analysing the bulk of the available literature, it needs to be remembered that the evidence provided by this form of secondary research is only as good as the quality of the primary studies. This study was necessary to highlight the several methodological issues which exist in the currently available literature. At the moment the majority of the evidence comes from retrospective studies that by nature of their design are liable to methodological problems and bias.

There is, therefore, an urgent need to collect high-quality data that include a detailed description of various confounding variables such as size, number, location (confirmed by accurate methods), age, body mass index and cause of infertility. The answer should come from a multicentre study of sufficient power and quality.

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