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META-ANALYSIS *Infertility*

The effect of intramural fibroids without uterine cavity involvement on the outcome of IVF treatment: a systematic review and meta-analysis

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BACKGROUND: The influence of fibroids on fertility is poorly understood. Submucosal and intramural fibroids that distort the endometrial cavity have been associated with decreased pregnancy rates (PRs) following IVF treatment. However, there is uncertainty about the effect of intramural fibroids that do not distort the endometrial cavity on IVF outcomes.

METHODS: We conducted a systematic review and meta-analysis of studies to evaluate the association between non-cavity-distorting intramural fibroids and IVF outcome. Searches were conducted on MEDLINE, EMBASE, Cochrane Library and Web of Science. Study selection and data extraction were conducted independently by two reviewers. The Newcastle-Ottawa Quality Assessment Scales were used for quality assessment. Meta-analysis was performed if appropriate.

RESULTS: We identified 19 observational studies comprising 6087 IVF cycles. Meta-analysis of these studies showed a significant decrease in the live birth (RR = 0.79, 95% CI: 0.70–0.88, $P < 0.0001$) and clinical PRs (RR = 0.85, 95% CI: 0.77–0.94, $P = 0.002$) in women with non-cavity-distorting intramural fibroids compared with those without fibroids, following IVF treatment.

CONCLUSION: The presence of non-cavity-distorting intramural fibroids is associated with adverse pregnancy outcomes in women undergoing IVF treatment.

Key words: intramural fibroids / IVF / pregnancy / observational studies

Introduction

Uterine fibroids occur in up to 30% of reproductive age women (Verkauf, 1992) and are more common in Afrocarribean women. Although most women affected with fibroids are fertile, fibroids may interfere with fertility secondary to anatomical distortion and alterations to the uterine environment (Hasan *et al*., 1990; Verkauf, 1992), with the effect being dictated largely by the location and size of the fibroid (Ubaldi *et al*., 1995; Rackow and Arici, 2005).

With regards to *in vitro* fertilization (IVF) treatment, submucosal and intramural fibroids that protrude into the endometrial cavity have been associated with decreased pregnancy rates (PRs) and implantation rates (IRs) (Narayan and Goswamy, 1994; Farhi *et al*., 1995; Varasteh *et al*., 1999; Bernard *et al*., 2000). Studies have shown that IVF outcome is markedly improved in women with cavity-distorting submucosal fibroids following myomectomy (Narayan and Goswamy, 1994; Varasteh *et al*., 1999; Bernard *et al*., 2000; Hart *et al*., 2001; Surrey *et al*., 2005). However, the effect of fibroids not distorting the uterine cavity on the outcome of IVF treatment remains poorly understood with studies yielding conflicting results. The conflicting results may be attributable to clinical heterogeneity between the studies such as differences in patient inclusion criteria, and methodological inconsistencies related to the design of the studies. We conducted a systematic review of studies evaluating the association between non-cavity-distorting intramural fibroids and IVF outcome, and attempted to explore the inconsistencies present in the literature.

Methods

Identification of literature

The following electronic databases were searched: MEDLINE (1950 to October 2008), EMBASE (1980 to October 2008), Cochrane Central Register of Controlled Trials and Web of Science (1990 to October 2008). A combination of Medical Subject Headings (MeSH) and text words were used to generate two subsets of citations, one including studies of uterine fibroids ('uterine fibroids', 'leiomyomas', 'myomas') and the other including studies of *in vitro* fertilization and intracytoplasmic sperm injection ('*in vitro* fertilization', 'fertilization-*in vitro*', 'intracytoplasmic sperm injection', 'sperm injection intracytoplasmic', 'reproductive techniques assisted', 'embryo transfer' and 'embryo implantation'). These subsets were combined with 'AND' to generate a subset of citations relevant to our research question. The reference lists of all known primary and review articles were examined to identify cited articles not captured by electronic searches. Articles, which were frequently quoted, were used in the Science Citation Index to identify additional citations. We also made enquires about unpublished studies from researchers investigating in this field. No language restrictions were placed in any of our searches. The searches were conducted independently by S.K.S. and M.K.

Study selection and data extraction

Studies were selected if the target population was women undergoing IVF treatment with or without ICSI, and the exposure was the presence of non-cavity-distorting intramural fibroids in the study group and no fibroids in the control group (no exposure). Studies involving women with submucous fibroids or predominantly subserous fibroids were excluded. The primary outcome of interest was the live birth rate. We also reported on secondary outcome measures such as clinical PR, IR and miscarriage rate.

Studies were selected in a two-stage process. First, the titles and abstracts from the electronic searches were scrutinized by two reviewers independently (S.K.S. and M.K.) and full manuscripts of all citations that were likely to meet the predefined selection criteria were obtained. Secondly, final inclusion or exclusion decisions were made on examination of the full manuscripts. In cases of duplicates the most recent or the most complete publication was used. Any disagreements about inclusion were resolved by consensus or arbitration by a third reviewer (A.C.).

Two reviewers (S.K.S. and M.K.) completed the quality assessment (Berlin and Rennie, 1999). The Newcastle-Ottawa Quality Assessment Scales for observational studies were implemented (Wells *et al.*, 2000). Items assessed included selection of cases/cohorts and controls, comparability and exposure/outcome. We used an arbitrary score based on the assumption of equal weight of all items included in the Newcastle-Ottawa Scale. This was used to give a quantitative appraisal of overall quality of the individual studies. The score ranged from 0 to 9, with a score of either 0 or 1 for each item. From each study, outcome data were extracted in 2 × 2 tables by the two reviewers S.K.S. and M.K.

Statistical analysis

Relative risks from individual studies were meta-analysed using fixed effects model (Mantel and Haenszel, 1959) and random effects models as appropriate (DerSimonian and Laird, 1986). Heterogeneity of the exposure effects was evaluated graphically using forest plots (Lewis and Clarke, 2001) and statistically using the I^2 statistic to quantify heterogeneity across studies (Higgins and Thompson, 2002). Exploration of the causes of heterogeneity was planned using variation in features of population, exposure and study quality. We performed sensitivity analyses where possible and appropriate to address the clinical and methodological variations. To assess for publication bias we performed funnel plot analysis, using Egger's test to test for asymmetry for the primary outcome of live birth (Egger *et al.*, 1997). Statistical analyses were performed using RevMan 4.2 (Cochrane Collaboration, Oxford, UK) and Stata 8.0 (Stata Corp, TX, USA).

Results

The search strategy yielded 805 citations, all captured from electronic citations (Fig. 1). Of these, 704 publications were excluded as it was clear from the title that they did not fulfil the selection criteria. From the remaining 101 articles, 74 were excluded on the basis of the abstract. For the remaining 27 articles, we obtained full manuscripts, and following scrutiny of these, we identified 24 potentially relevant studies; three publications were excluded as they were either duplicates and/or the same data were used in other included studies (Healy, 2000; Hart *et al.*, 2001; Oliveira *et al.*, 2005). From these 24 studies, five were excluded for the following reasons: one study included women with intramural and/or submucous fibroids and did not report data separately for women with only intramural fibroids (Gianaroli *et al.*, 2005); two studies involved women with predominantly subserous fibroids (Seoud *et al.*, 1992; Ramzy *et al.*, 1998); one study did not specify whether the fibroids were intramural or subserous (Farhi *et al.*, 1995); and another study was excluded as the aim of this study was to establish the impact of surgical removal of fibroids before IVF treatment where women in the treatment group had myomectomy and women in the control group did not have surgery (Bulletti *et al.*, 2004). Therefore the total number of studies included in the review was 19 (Fig. 1). Of these studies, 18 studies were in English and one study was in Spanish (Manzo *et al.*, 2006); 18 studies were full manuscripts and one was an abstract (Bozdag *et al.*, 2009), the full article of which is in press. We obtained as much information as possible from the authors of this manuscript so that we could include the study in our review.

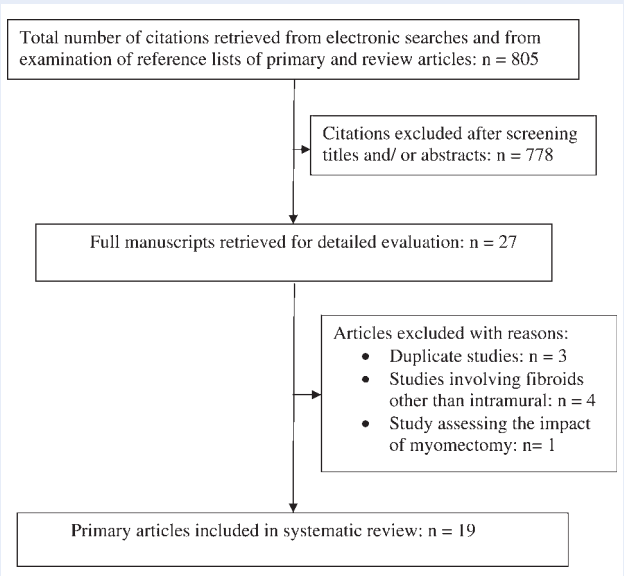

Figure 1 Study selection process for systematic review on the effect of non-cavity-distorting intramural fibroids on IVF treatment outcome.

All of the 19 included studies were observational studies whereby the target population (women having IVF treatment), with or without non-cavity-distorting intramural fibroids (exposure) were followed up to the outcomes. The main characteristics of the 19 studies and the Newcastle-Ottawa Quality Assessment are presented in Tables I and II. Although all studies included women with either only or predominantly non-cavity-distorting intramural fibroids, the size and number of fibroids varied. The exclusion criteria also varied between the different studies (Table I). In four of the studies (Dietterich *et al*., 2000; Wang and Check, 2004; Klatsky *et al*., 2007; Horcajadas *et al*., 2008), the women had oocyte donation IVF treatment. The studies scored well on the Newcastle-Ottawa Quality Assessment Scale (Table II); 1 study had the maximum score of 9, 16 studies scored 8 and 2 studies scored 7. Funnel plot analysis indicated that publication and related biases were unlikely (Egger's test $P = 0.98$, Fig. 2).

Primary outcome

Live birth rate

Pooling of results from 11 of the 19 studies that reported live birth as an outcome showed a statistically significant 21% relative reduction in live birth rate in women with non-cavity-distorting intramural fibroids compared with women without fibroids (RR = 0.79, 95% CI: 0.70–0.88, $P < 0.0001$, Fig. 3). The finding remained unaltered regardless of the statistical method for pooling, with fixed (Mantel and Haenszel, 1959) or random (DerSimonian and Laird, 1986) effects models. The I^2 value was 15.1% indicating little variability in live birth between the studies.

Meta-analysis of the eight studies in which the mean age of women was less than 37 years and of the four studies involving women having their first IVF treatment cycle and that reported live birth as an outcome showed a significant 25% relative reduction and a non-significant 23% relative reduction, respectively, in live birth rate in women with intramural fibroids (RR = 0.75, 95% CI: 0.62–0.89, $P = 0.001$, Fig. 4 and RR = 0.77, 95% CI: 0.59–1.00, $P = 0.05$, Fig. 5). The I^2 values were 31.9 and 52.4%, respectively, indicating significant heterogeneity.

Pooled analysis of the two prospective studies that reported live birth as an outcome showed a 40% significant relative reduction in live birth rate in women with intramural fibroids (RR = 0.60, 95% CI: 0.41–0.87, $P = 0.007$, Fig. 6). There was no inconsistency between the studies, as indicated by an I^2 value of 0%.

Secondary outcomes

Clinical PR

Pooling of results from 18 of the 19 studies that reported clinical pregnancy as an outcome showed a statistically significant 15% reduction in clinical PR in women with non-cavity-distorting intramural fibroids, following IVF treatment (RR = 0.85, 95% CI: 0.77–0.94, $P = 0.002$, Fig. 7). There was significant inconsistency across studies as indicated by an I^2 value of 25.7%.

Meta-analysis of the 13 studies that reported clinical pregnancy as an outcome in which the mean age of the women was less than 37 years showed a significant 18% reduction in the clinical PR in women with intramural fibroids (RR = 0.82, 95% CI: 0.73–0.92, $P = 0.0005$). The I^2 value was 11% indicating little variation among these studies for the outcome of clinical pregnancy. Meta-analysis of the six studies that included women having their first IVF treatment cycle showed a significant 16% relative reduction in the clinical PR in women with intramural fibroids (RR = 0.84, 95% CI: 0.73–0.96, $P = 0.009$). The I^2 value was 22.3% indicating little variation among the studies.

Pooling of results of the four prospective studies that reported clinical PR as an outcome showed a 11% non-significant reduction in clinical PR in women with intramural fibroids following IVF treatment (RR = 0.89, 95% CI: 0.68–1.17, $P = 0.41$). There was no inconsistency among these studies as indicated by an I^2 value of 0%.

Implantation rate

Meta-analysis for the secondary outcome of IR showed a statistically non-significant 13% reduction in IR in women with non-cavity-distorting intramural fibroids (RR = 0.87, 95% CI: 0.73–1.03, $P = 0.11$, Fig. 8). There was significant inconsistency across the nine relevant studies (I^2=26.3%).

Meta-analysis of the six studies involving women with a mean age of less than 37 years and that reported IR as an outcome showed a significant 28% reduction in IR in women with intramural fibroids (RR = 0.72, 95% CI: 0.59–0.87, $P = 0.0006$). The I^2 value was 0% indicating statistical homogeneity across studies. Two of the six studies involving women having their first IVF treatment cycle reported IR as an outcome. Meta-analysis of the two studies showed a non-significant 16% reduction in IR in women with intramural fibroids (RR = 0.84, 95% CI: 0.55–1.29, $P = 0.42$). The I^2 value was 0% indicating statistical homogeneity across these studies.

Two prospective studies (Ng *et al*., 2005; Khalaf *et al*., 2006) reported IR as an outcome. The results of these two studies could not be pooled as one of the studies reported the outcome in terms of odds ratio (Khalaf *et al*., 2006). Both studies showed a trend towards a reduction in IR in women with intramural fibroids following IVF treatment, although the individual results were not statistically significant.

Miscarriage rate

Pooling of all studies that reported miscarriage as an outcome showed a statistically non-significant 24% relative increase in miscarriage rate in women with non-cavity-distorting intramural fibroids, following IVF treatment (RR = 1.24, 95% CI: 0.99–1.57, $P = 0.07$, Fig. 9). There was little inconsistency across studies with an I^2 value of 11.1%.

Meta-analysis of the 10 studies that reported miscarriage as an outcome in which the mean age of women was less than 37 years and of the six studies involving women having their first IVF treatment cycle showed non-significant 5 and 15% relative increases, respectively, in the miscarriage rate in women with intramural fibroids (RR = 1.05, 95% CI: 0.80–1.39, $P = 0.73$ and RR = 1.15, 95% CI: 0.82–1.60, $P = 0.43$ respectively). The I^2 value was 0% in both the analyses indicating statistical homogeneity across studies. Meta-analysis of the three prospective studies that reported miscarriage as an outcome showed a 10% non-significant relative increase in miscarriage rate in women with intramural fibroids (RR = 1.10, 95% CI: 0.55–2.19, $P = 0.80$). There was little variation among the studies, as the I^2 value was 7.3%.

Table I Characteristics of studies of non-cavity-distorting intramural fibroids versus no fibroids on IVF treatment outcome

Study	Type of study	Inclusion criteria	Exclusion criteria	Study groups	Fibroids size and number	Outcome measure
Eldar-Geva *et al.* (1998) ($n = 378$)	Retrospective comparative study	Women undergoing IVF treatment with non-cavity-distorting intramural fibroids and matched controls without fibroids.	Women with previous myomectomy or other uterine anomalies (septae or polyps).	Study group ($n = 55$), with non-cavity-distorting intramural fibroids. Controls ($n = 318$), matched for age.	Fibroids size ranging from 0.6 to 5.1 cm. Number of fibroids ranging from 1 to 7.	IR Clinical PR Miscarriage rate Ectopic PR Live birth rate
Stovall *et al.* (1998) ($n = 182$)	Retrospective matched control study	Women undergoing their first IVF treatment with non-cavity-distorting intramural fibroids and subserous fibroids and matched consecutive controls without fibroids.*	Women undergoing oocyte donation or frozen embryo transfer.	Study group ($n = 91$), most with non-cavity-distorting intramural fibroids. Controls ($n = 91$), matched for age, number of embryos transferred and grade of embryos.	Fibroids size ranging from 8 to 54 mm. Mean number of fibroids per patient 1.8 ± 0.8.	IR Clinical PR Miscarriage rate Ectopic PR Live birth rate
Rinehart (1999) ($n = 48$)	Retrospective case–control study	Women undergoing IVF treatment with non-cavity-distorting intramural fibroids and matched controls without fibroids.	Women with fibroids impinging on the uterine cavity.	Patients ($n = 24$), with non-cavity-distorting intramural fibroids. Controls ($n = 24$), matched for age, stimulation protocol and type of micromanipulation.	Fibroids size ranging from 5 to 32.5 mm. Number of fibroids ranging from 1 to 5.	IR Clinical PR
Dietterich *et al.* (2000) ($n = 20$)	Retrospective comparative study	Women (>35 years) undergoing their first donor oocyte IVF treatment with non-cavity-distorting fibroids and controls undergoing similar treatment without fibroids.	Women with previous myomectomy, uterine cavity abnormalities, uterine cavity distortion by fibroids or prior pregnancy through treatment at the study centre.	Study group ($n = 9$), with non-cavity-distorting intramural fibroids. Controls ($n = 11$).	Fibroids size ranging from 0.6 to 2.6 cm. Number of fibroids ranging from 1 to 6.	IR Clinical PR Multiple PR
Jun *et al.* (2001) ($n = 547$)	Retrospective comparative study	Women undergoing their first IVF treatment with non-cavity-distorting intramural or subserous fibroids and controls without fibroids.†	Women undergoing oocyte donation, surrogacy and frozen embryo transfer. Women with previous myomectomy and no fibroids on ultrasound scan were included in the control group.	Study group ($n = 141$), most with non-cavity-distorting intramural fibroids. Controls ($n = 406$).	Fibroids with mean size 1.93 ± 1.26 cm and all fibroids <7 cm.	Clinical PR Miscarriage rate Ectopic PR Live birth rate
Surrey *et al.* (2001) ($n = 400$)	Retrospective case–control study	Women undergoing IVF treatment with non-cavity-distorting intramural fibroids controls without fibroids.	Patients with previous myomectomy, submucous and subserous fibroids.	Study group ($n = 73$), with non-cavity-distorting intramural fibroids. Controls ($n = 327$).		IR Clinical PR Live birth rate

Continued

Table I *Continued*

Study	Type of study	Inclusion criteria	Exclusion criteria	Study groups	Fibroids size and number	Outcome measure
Check *et al.* (2002) ($n = 182$)	Prospective matched control study	Women undergoing their first IVF treatment with non-cavity-distorting intramural fibroids and matched controls without fibroids.	Women with intramural fibroids >5 cm, submucous fibroids, uterine cavity abnormalities or previous myomectomy or other uterine surgery.	Study group ($n = 61$), with non-cavity-distorting intramural fibroids.	Fibroids size ranging from 0.5 to 3.8 cm. Number of fibroids ranging from 1 to 7. Controls ($n = 61$) matched for age.	Clinical PR Miscarriage rate Ectopic PR Live birth rate
Yarali and Bukulmez (2002) ($n = 397$)	Retrospective case–control study	Women undergoing their first ICSI treatment with non-cavity-distorting intramural fibroids and matched controls without fibroids.	Women with fibroids >10 cm. None of them had a previous myomectomy.	Study group ($n = 73$), with non-cavity-distorting intramural fibroids. Controls ($n = 324$) matched for age and body mass index.	Average size of fibroid 3.0 ± 1.8 cm. Mean number of fibroids 3.1 ± 2.0.	IR Clinical PR Miscarriage rate Multiple PR
Aboulghar *et al.* (2004) ($n = 133$)	Prospective matched control study	Women undergoing IVF treatment with intramural fibroids >5 mm from the endometrium and matched controls without fibroids.‡	Women with fibroids <5 mm from the endometrial lining, submucous fibroids and fibroid polyps.	Study group ($n = 33$), with intramural fibroids >5 mm from the endometrium. Controls ($n = 100$) matched for age.		Clinical PR
Oliveira *et al.* (2004) ($n = 408$)	Retrospective matched control study	Patients undergoing their first IVF treatment with non-cavity-distorting intramural fibroids and matched controls with no fibroids.	Women with uterine cavity distortion by fibroids, fibroids >7 cm, or previous myomectomy.	Study group ($n = 163$), with non-cavity-distorting intramural fibroids. Controls ($n = 245$), matched for age and number of oocytes retrieved.	Average size of fibroid ranging from 0.4 to 6.9 cm. Number of fibroids ranging from 1 to 4.	Clinical PR Miscarriage rate Multiple PR Preterm delivery rate Live birth rate
Wang and Check (2004) ($n = 122$)	Retrospective comparative study	Women undergoing their first donor oocyte IVF treatment with intramural or subserous fibroids and controls undergoing similar treatment without fibroids.	Women with uterine abnormalities, previous history of polyps, uterine septae, myomectomy, presence of submucous or pedunculated fibroids.	Study group ($n = 49$), with non-cavity-distorting intramural and subserous fibroids. Controls ($n = 73$).	Maximum average size of fibroid 3.3 cm	IR Clinical PR Miscarriage rate Live birth rate
Ng *et al.* (2005) ($n = 100$)	Prospective matched control study	Women undergoing IVF treatment with non-cavity-distorting intramural fibroids and matched consecutive controls without fibroids.	Women with previous myomectomy, fibroids causing uterine cavity distortion, smokers and those with estradiol level >20 000 pmol/l on the day of transvgainal oocyte retrieval.	Study group ($n = 50$), with non-cavity-distorting intramural fibroids.	Median volume of fibroids 6.8 cm^3. Number of fibroids ranging from 1 to 6. Controls ($n = 50$) matched for age, type of infertility and serum E2 concentrations.	IR Clinical PR Miscarriage rate
Khalaf *et al.* (2006) ($n = 434$)	Prospective comparative study	Women undergoing their first three cycles of IVF treatment in 12 months with non-cavity-distorting intramural fibroids and controls without fibroids	Women undergoing oocyte donation, surrogacy and frozen embryo transfer, fibroids >5 cm, fibroids distorting the uterine cavity or previous myomectomy.	Study group ($n = 112$), with non-cavity-distorting intramural fibroids. Control s ($n = 322$), were 2 years younger than the study group but had similar baseline characteristics.	Mean size of fibroids 2.3 ± 1.1 cm. Mean number 1.8 ± 0.8.	IR Ongoing PR

Manzo *et al.* (2006) ($n = 431$)	Retrospective comparative study	Women undergoing IVF treatment with non-cavity-distorting intramural fibroids and subserous fibroids and controls without fibroids.[§]	Women with fibroids causing uterine cavity distortion.	Study group ($n = 65$), most with non-cavity-distorting intramural fibroids. Controls ($n = 366$), were 2 years younger than the study group but had similar baseline characteristics and IVF cycles parameters.	Fibroid size ranging from 2 to 5 cm.	Miscarriage rate Ectopic PR Multiple PR Preterm delivery rate Live birth rate
Klatsky *et al.* (2007) ($n = 344$)	Retrospective cohort study	Women undergoing their first donor oocyte IVF treatment with non-cavity-distorting intramural or subserous fibroids and matched controls without fibroids undergoing similar treatment.**	Women with no data on donor age, number of embryos transferred, adenomyosis, mullerian abnormalities or cycles cancelled because of poor endometrial thickness.	Study group ($n = 94$), most with non-cavity-distorting intramural fibroids. Controls ($n = 275$), matched for donor age, number of embryos transferred, endometrial thickness, and recipient BMI.	Average diameter of fibroids 2.8 cm. 36% had more than one fibroid.	IR Clinical PR Miscarriage rate
Nejad *et al.* (2007) ($n = 278$)	Prospective cohort study	Women <38 years undergoing their first IVF/ICSI treatment, with non-cavity-distorting intramural fibroids and age matched controls without intramural fibroids.	Women undergoing IVF/ICSI, oocyte donation and frozen embryo transfer, fibroids >6 cm, fibroids distorting the uterine cavity, previous myomectomy and those prone to ovarian hyperstimulation syndrome.	Study group ($n = 94$), with non-cavity-distorting intramural fibroids. Controls ($n = 184$) matched for age.	Fibroid size <3 cm in 55.3% and 3–6 cm in 44.7% of women. Single fibroid in 21.4% and multiple fibroids 78.6% of women.	Clinical PR Miscarriage rate
Vimercati *et al.* (2007) ($n = 236$)	Retrospective comparative study	Women undergoing IVF and ICSI treatment with non-cavity-distorting intramural fibroids controls without fibroids.	Women with previous myomectomy.	Study group ($n = 31$), with non-cavity-distorting intramural fibroids. Controls ($n = 205$).		IR Clinical PR Miscarriage rate Ectopic PR Multiple PR Ongoing PR
Horcajadas *et al.* (2008) ($n = 942$)	Retrospective study; hybrid design between case and control and cohort study	Women undergoing their first donor oocyte IVF treatment with non-cavity-distorting intramural fibroids and controls without fibroids undergoing similar treatment.	Women with adenomyosis/ endometriosis previous uterine surgery, myomectomy and couples with severe oligozoospermia.	Study group ($n = 807$), with non-cavity-distorting intramural fibroids. Controls ($n = 135$).	Size of fibroid ranging from 0.4 to 8.09 cm. Number of fibroids ranging from 1 to 3.	IR Miscarriage rate Multiple PR Ongoing PR Live birth rate
Bozdag *et al.* (in press) ($n = 505$)	Retrospective matched control study	Women undergoing ICSI treatment with a single non-cavity-distorting intramural fibroid and matched controls without fibroids.	Women with more than one non-cavity-distorting intramural fibroid.	Study group ($n = 61$), with a single non-cavity-distorting intramural fibroid. Controls ($n = 444$) matched for age.		IR Clinical PR Miscarriage rate

*94.5% had intramural fibroids.
†87.9% had intramural fibroids.
‡Authors when contacted clarified that fibroids >5 mm from endometrium did not distort the endometrial cavity.
§86% of women had intramural fibroids.
**73% of women had intramural fibroids.

Table II Appraisal of methodological quality (Newcastle-Ottawa Scale)

Study	Case–cohort representative	Selection of non-exposed control	Ascertainment of exposure	Outcome negative at start	Comparability by design	Comparability by analysis	Outcome assessment	Duration of follow-up	Adequacy of follow-up	Score
Eldar-Geva *et al.* (1998)	*	*	*	*	*	x	*	*	*	8
Stovall *et al.* (1998)	*	*	*	*	*	x	*	*	*	8
Rinehart (1999)	*	*	*	*	*	x	*	*	*	8
Dietterich *et al.* (2000)	*	*	*	*	x	x	*	*	*	7
Jun *et al.* (2001)	*	*	*	*	x	*	*	*	*	8
Surrey *et al.* (2001)	*	*	*	*	*	*	*	*	*	9
Check *et al.* (2002)	*	*	*	*	*	x	*	*	*	8
Yarali and Bukulmez (2002)	*	*	*	*	*	x	*	*	*	8
Aboulghar *et al.* (2004)	*	*	*	*	*	x	*	*	*	8
Oliveira *et al.* (2004)	*	*	*	*	*	x	*	*	*	8
Wang and Check (2004)	*	*	*	*	x	x	*	*	*	7
Ng *et al.* (2005)	*	*	*	*	*	x	*	*	*	8
Khalaf *et al.* (2006)	*	*	*	*	x	*	*	*	*	8
Manzo *et al.* (2006)	*	*	*	*	x	*	*	*	*	8
Klatsky *et al.* (2007)	*	*	*	*	x	*	*	*	*	8
Nejad *et al.* (2007)	*	*	*	*	*	x	*	*	*	8
Vimercati *et al.* (2007)	*	*	*	*	x	*	*	*	*	8
Horcajadas *et al.* (2008)	*	*	*	*	x	*	*	*	*	8
Bozdag *et al.* (in press)	*	*	*	*	*	x	*	*	*	8

* = 1 (adequate), x = 0 (not adequate/unclear).

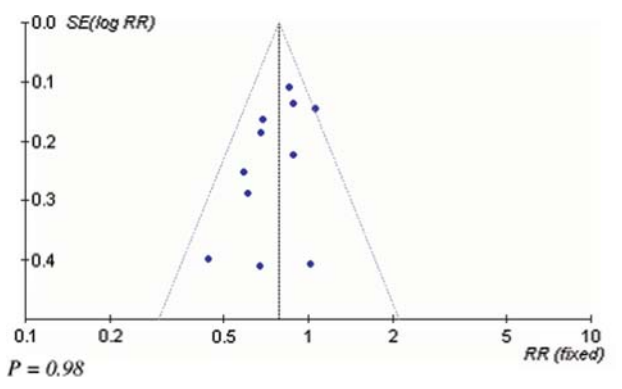

Figure 2 Funnel plot for publication bias for outcome of live birth rates: treatment effects (x-axis) versus study size (y-axis).

Discussion

This systematic review, which included 6087 IVF cycles, found that the presence of non-cavity distorting intramural fibroids on average reduces the live birth rate by 21% and the clinical PR by 15% per IVF cycle compared with no fibroids. The relatively lower chance of achieving a live birth compared with clinical pregnancy probably reflects the adverse influence of intramural fibroids on the course of pregnancy (Khaund and Lumsden, 2008; Klatsky *et al*., 2008).

The inverse relationship between IVF outcome and the presence of non-cavity distorting intramural fibroid may be explained by altered uterine vascular perfusion, myometrial contractility, endometrial function, gamete migration or myometrial/endometrial gene expression (Arslan *et al*., 2005; Ng *et al*., 2005; Nishino *et al*., 2005; Pritts *et al*., 2009). Previous reviews have addressed the relationship between intramural fibroids and outcome of IVF treatment (Somigliana *et al*., 2007; Klatsky *et al*., 2008; Pritts *et al*., 2009). The results of our systematic review are concordant with the findings of

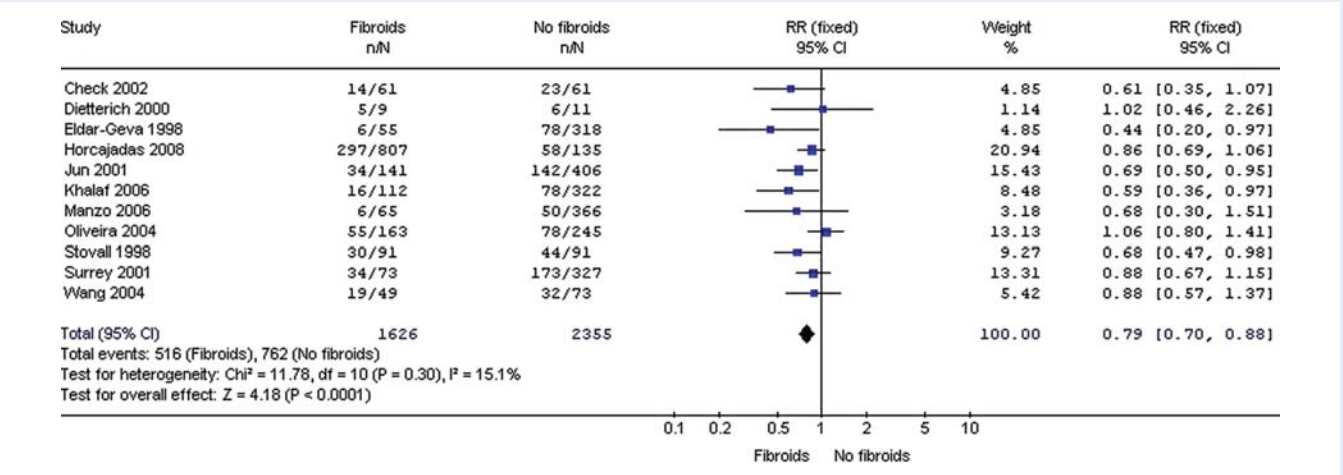

Figure 3 Forest plot of studies of non-cavity-distorting intramural fibroids versus no fibroids in women undergoing IVF treatment for outcome of live birth rates.

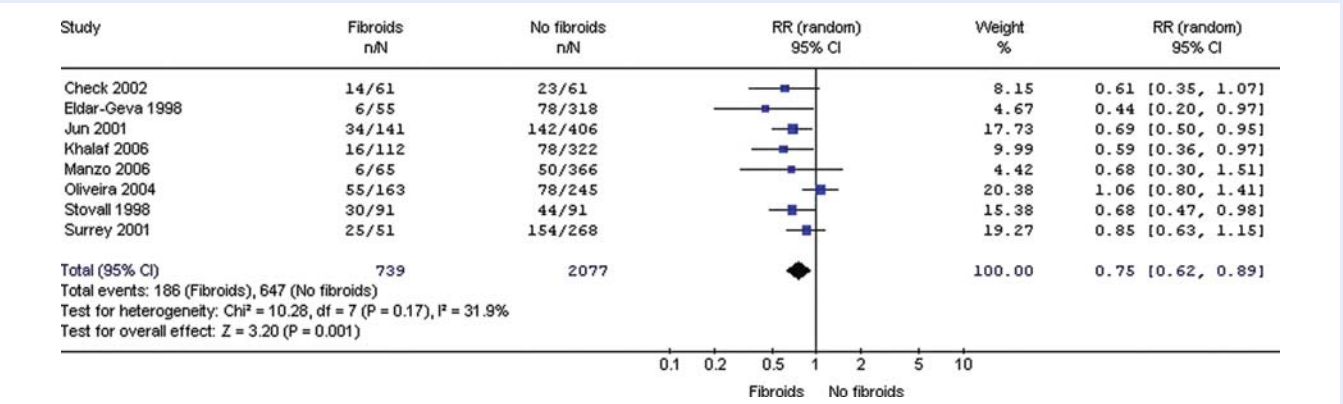

Figure 4 Forest plot of studies of non-cavity-distorting intramural fibroids versus no fibroids in women <37 years undergoing IVF treatment for outcome of live birth rates.

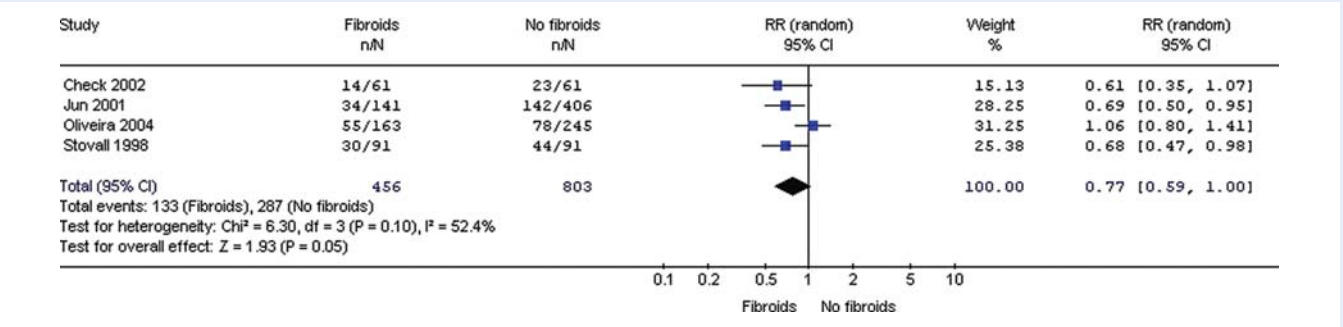

Figure 5 Forest plot of studies of non-cavity-distorting intramural fibroids versus no fibroids in women undergoing their first IVF treatment for outcome of live birth rates.

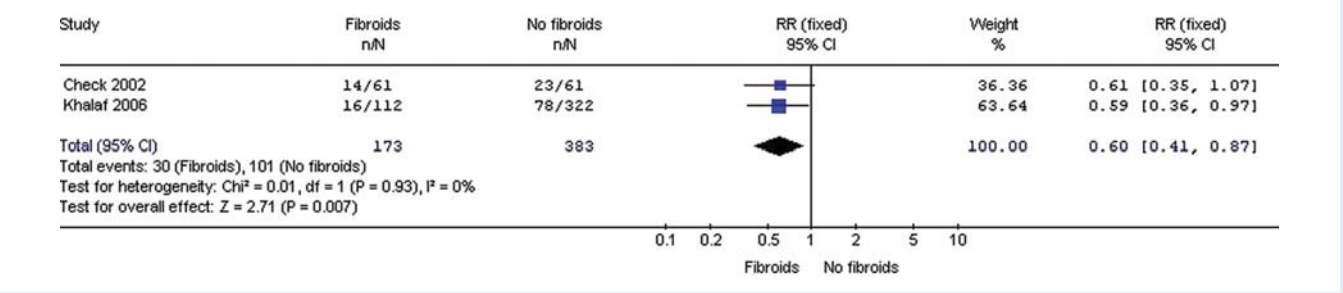

Figure 6 Forest plot of prospective studies of non-cavity-distorting intramural fibroids versus no fibroids in women undergoing IVF treatment for outcome of live birth rates.

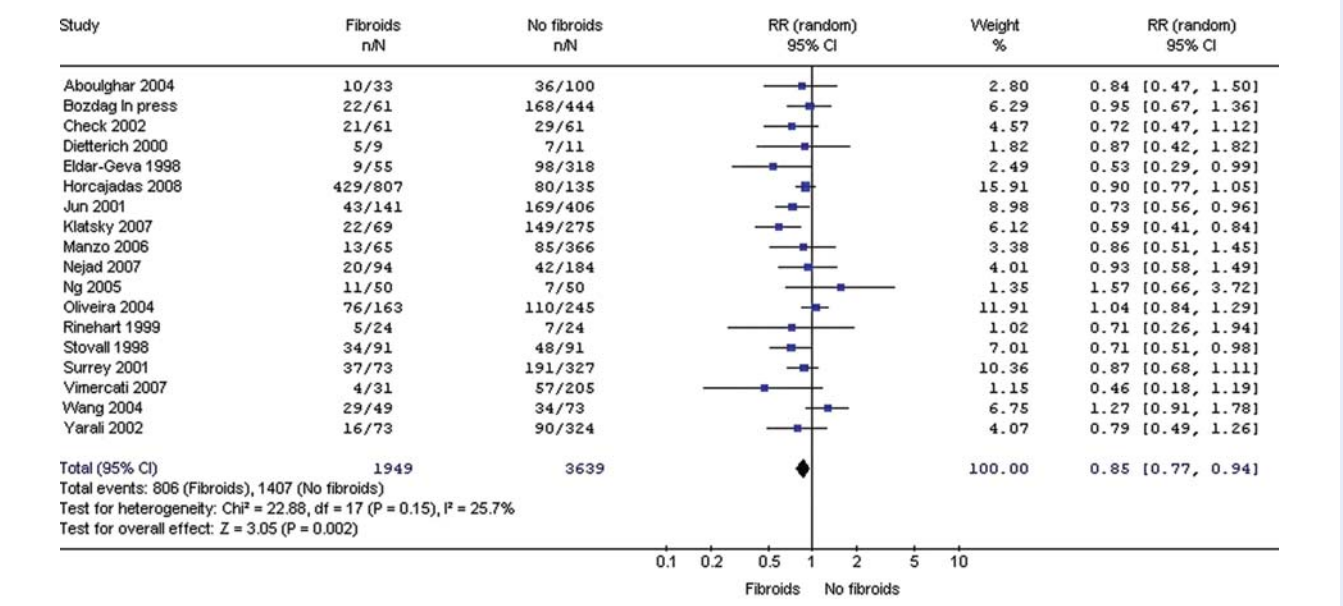

Figure 7 Forest plot of studies of non-cavity-distorting intramural fibroids versus no fibroids in women undergoing IVF treatment for outcome of clinical PRs.

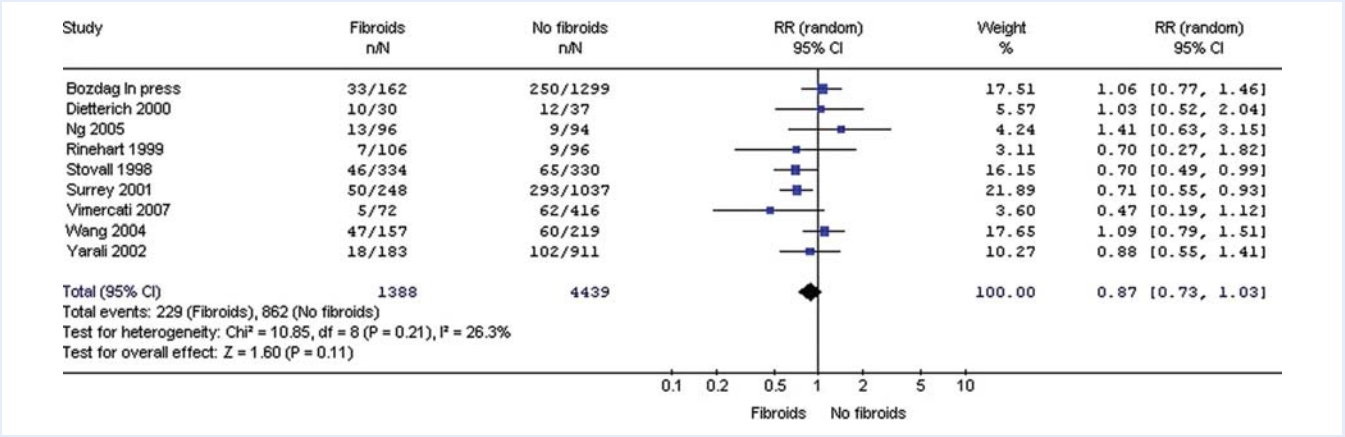

Figure 8 Forest plot of studies of non-cavity-distorting intramural fibroids versus no fibroids in women undergoing IVF treatment for outcome of IRs.

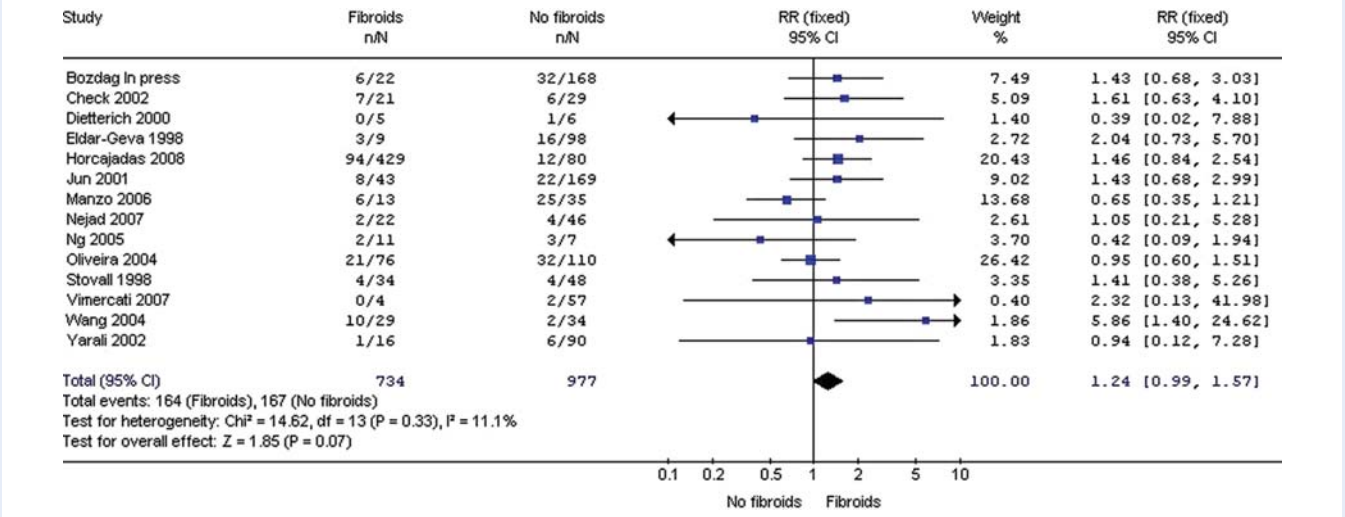

Figure 9 Forest plot of studies of non-cavity-distorting intramural fibroids versus no fibroids in women undergoing IVF treatment for outcome of miscarriage rates.

the recent updated review by Pritts *et al*. (2009) which addressed the impact of submucosal, intramural and subserosal fibroids on fertility. Our review represents the first attempt to extensively review the literature and provide a quantitative estimate of the relationship between non-cavity distorting intramural fibroids and IVF outcome.

The strength of our review lies in the extensive search strategy and valid data synthesis methods. We also contacted authors of the primary studies for clarification of relevant information. We performed a funnel plot analysis to assess the publication bias. The funnel plot was symmetrical, indicating that publication and related biases were unlikely. The validity of our results is also directly related to the quality of the primary studies selected through our search. We used the Newcastle-Ottawa Quality Assessment Scale to rate the quality of the included studies (Table II). Individual studies scored well on the Quality Assessment Scale. The studies included varied in the design; 14 of the 19 studies were retrospective studies and 5 were prospective studies (Table I).

The weaknesses in our review are mainly related to the clinical heterogeneity among the studies. For example the nature of IVF treatment provided varied amongst the primary studies, with six studies assessing the impact of intramural fibroids on the first IVF/ ICSI cycle (Stovall *et al*., 1998; Jun *et al*. 2001; Check *et al*., 2002; Nejad *et al*., 2007; Yarali and Bukulmez 2002; Oliveira *et al*., 2004), four other studies examined the effect of intramural fibroids in oocyte donation cycles (Dietterich *et al*., 2000; Wang and Check, 2004; Klatsky *et al*., 2007; Horcajadas *et al*., 2008) and one study reporting the cumulative IVF outcome after a maximum of three IVF/ICSI cycles (Khalaf *et al*., 2006). Studies also differed in the diagnostic methods used to ascertain normality of the uterine cavity. Whilst some studies used ultrasound scan only, others used additional

hysterosonography, hysterosalpingography or hysteroscopy to exclude uterine cavity distortion. The mean size and number of fibroids also varied across the studies. Moreover, whereas some studies excluded women with previous myomectomy, others did not mention excluding them, and one study (Jun *et al*., 2001) included women with previous myomectomy and no fibroids on ultrasound scan in the control group.

To address the clinical heterogeneity, we performed multiple sensitivity analyses based on age, order of treatment cycle and design of study for both primary and secondary outcomes. Meta-analysis of studies that involved women with mean age less than 37 years showed an adverse effect on pregnancy outcomes in women with intramural fibroids following IVF treatment. Meta-analysis of studies only involving women having their first IVF treatment cycle was also consistent in showing a negative impact on pregnancy outcomes. Meta-analysis of only the prospective studies also showed an adverse pregnancy outcome following IVF treatment in women with intramural fibroids compared with women without fibroids, with a 40% significant reduction in live birth rate.

In conclusion, although this review of observational studies found a reduced chance of IVF success associated with the presence of non-cavity-distorting intramural fibroids, it should be acknowledged that observational studies are fraught with potential biases and confounders. Moreover, demonstration of reduction in IVF live births in women with non-cavity-distorting intramural fibroids does not necessarily mean that removal of such fibroids will restore the live birth rates to the levels expected in women without fibroids. Therefore this evidence does not justify advocating routine myomectomy for these women, as a favourable risk benefit analysis of this surgical intervention or any other interventions, in this clinical context is currently lacking. A well designed randomized controlled trial is therefore needed to address this question and generate the best evidence overcoming the pitfalls of observational studies.

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