Fibroids and infertility: an updated systematic review of the evidence

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Objective: To investigate the effect of fibroids on fertility and of myomectomy in improving outcomes.
Design: Systematic literature review and meta-analysis of existing controlled studies.
Setting: Private center for Reproductive endocrinology and infertility.
Patient(s): Women with fibroids and infertility.
Intervention(s): A systematic literature review, raw data extraction and data analysis.
Main Outcome Measure(s): Clinical pregnancy rate, spontaneous abortion rate, ongoing pregnancy/live birth rate, implantation rate, and preterm delivery rate in women with and without fibroids, and in women who underwent myomectomy.
Result(s): Women with subserosal fibroids had no differences in their fertility outcomes compared with infertile controls with no myomas, and myomectomy did not change these outcomes compared with women with fibroids in situ. Women with intramural fibroids appear to have decreased fertility and increased pregnancy loss compared with women without such tumors, but study quality is poor. Myomectomy does not significantly increase the clinical pregnancy and live birth rates, but the data are scarce. Fibroids with a submucosal component led to decreased clinical pregnancy and implantation rates compared with infertile control subjects. Removal of submucous myomas appears likely to improve fertility.
Conclusion(s): Fertility outcomes are decreased in women with submucosal fibroids, and removal seems to confer benefit. Subserosal fibroids do not affect fertility outcomes, and removal does not confer benefit. Intramural fibroids appear to decrease fertility, but the results of therapy are unclear. More high-quality studies need to be directed toward the value of myomectomy for intramural fibroids, focusing on issues such as size, number, and proximity to the endometrium. (Fertil Steril® 2009;91:1215–23. ©2009 by American Society for Reproductive Medicine.)

Key Words: Fibroids, infertility, myomectomy, ART, leiomyomata, fertility

The relationship between uterine fibroids and infertility has long been a concern to the gynecologic community, but the medical literature regarding this important topic is problematic. Uterine myomas are heterogeneous tumors in composition, size, location, and number; variations in any of these factors could possibly alter the effect on a woman's fertility status. Recommendations as to which infertile women with fibroids would benefit from myomectomy are varied, given the potential risks and sequelae of surgery. A number of studies have been performed to determine the influence of myomas on fertility, with widely disparate findings, and many of the studies suffer from methodologic flaws. The investigations are frequently poorly designed and often uncontrolled or historically controlled, analysis often lacks correction for important confounding variables, sample size is usually small, and conclusions are often provided that are unsupported by the data at hand.

In 2001, we performed a systematic review of controlled studies examining the issue of fibroids as a cause of infertility (1). Our analysis failed to demonstrate any effect of fibroids on fertility outcomes except when the tumors deformed the endometrial cavity. Since that time, numerous additional controlled studies have been published, some correcting for many of the shortcomings we noted in the previous analysis.

The present systematic review is designed to include these new studies along with the previously reviewed manuscripts to address two questions: 1) Do uterine fibroids, of specific size or location, decrease fertility?; and 2) does removal of the fibroid(s) enhance fertility?

MATERIALS AND METHODS

The MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines for systematic reviews of observational studies was used (2).

Received November 9, 2007; revised and accepted January 14, 2008; published online March 12, 2008.
The authors have nothing to disclose.
Presented in part at the annual meeting of the American Association of Gynecologic Laparoscopists, Chicago, Illinois, November 9–12, 2005.
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Search Strategy

PubMed, Ovid, and Cochrane Library databases were thoroughly searched using the key words "fibroid, leiomyomata, leiomyoma, infertility, ART, IVF." No limits were placed upon dates or language of publications. Only those studies with a control group were included. The subsequent bibliographies were cross-referenced. Hand searches of the proceedings for the years 1998–2004 were completed for the Society for Gynecologic Investigation, the American Society for Reproductive Medicine, the American Association of Gynecologic Laparoscopists, and the Pacific Coast Fertility Society in an attempt to identify any impending publications.

Relevance was initially evaluated from titles and then determined from abstracts. Full reports were reviewed for all potentially pertinent citations. Where more than one study was reported from the same center, authors were contacted to determine if the citations contained overlapping patients. If so, the later publication was chosen for inclusion.

Institutional Review Board approval was not provided, because it was determined that none was needed: All data used were abstracted from previously published studies.

The Studies

For a summary of each study analyzed, please refer to Table 1.

Of 347 studies initially evaluated, 23 were included in the data analysis (3–25). One randomized controlled treatment trial was identified (3), nine prospective studies were included (one matched, eight cohort) (5, 11–13, 15, 18–20, 22), and the remainder were retrospective. Inclusion required subjects actively attempting to conceive, and the use of an appropriate control group for the issue at hand. If raw data were unavailable, the authors were contacted and queried. Exclusion criteria included use of historical control groups and lack of control groups.

Eighteen published studies addressed the fundamental issue of whether fibroids reduce fertility and/or increase adverse pregnancy outcomes (4, 7, 9–11, 13–25). Seven studies examined the effect of myomectomy (3, 5, 6, 8, 12–14); three of these actually contained two study approaches within the publication (8, 13, 14). Thus, ten studies were available for assessing the value of treatment. Of these, only four compared myomectomy with fibroids left in situ (3, 12–14), with the remainder using infertile women without fibroids as the comparator. One study (13) used both approaches.

In 15 of the studies, the control groups were similar in age; however, three studies did not state the age of participants, in four studies the group with fibroids was significantly older than the control group, and in one study the control group was significantly older. In 15 of the reports, similar etiologies for infertility were apparent in the control groups. In eight publications this was not the case: Either the etiology of infertility in each group was not stated or there were clear differences in etiology and no statistical corrections were performed.

Methods of assisted reproduction in the included studies varied and included those undergoing in vitro fertilization with and without intracytoplasmic sperm injection, donor oocyte and/or embryo recipients, those receiving gonadotropins with intrauterine insemination, and some women attempting spontaneous conception.

Ten studies (4–12) included careful evaluation of the uterine cavity by either sonohysterogram or hysteroscopy to determine the presence of a submucosal or intracavitary fibroid. However, only four studies (6–9) used one of these methods in all study subjects. In the other studies, less accurate assessment with transvaginal sonography or hysterosalpingogram was used to evaluate the uterine cavity (3, 13–25).

In two studies (9, 25), subgroups of patients with either submucosal fibroids alone, or both intramural and submucosal fibroids, had hysteroscopic resection of the submucosal fibroids. These data were analyzed after resection as an infertile group with intramural fibroids compared with an infertile group without fibroids.

Data Extraction

Data were extracted from eligible studies as reported by the authors. Subjects were classified based upon their fibroid location whenever possible. All patients with tumors inside the endometrial cavity or causing intracavitary distortion were termed submucous (SM). Lesions not distorting the cavity but residing within myometrium were labeled intramural (IM). Those extending predominantly outside the myometrium were termed subserosal (SS). If individual subjects were noted to have both SM and IM fibroids, they were placed within the SM category for analytic purposes. Those individuals with both IM and SS fibroids were placed in the IM category. If women with either IM and SS fibroids were pooled within the report, they were not analyzed in either group but were included only when asking queries regarding SM versus "other" (i.e., noncavity-distorting fibroids).

Outcomes were recorded as clinical pregnancy, spontaneous abortion, or preterm delivery. Some studies reported ongoing pregnancies as those that had exceeded the first trimester, whereas others reported live births. These two outcomes were pooled into a single outcome measure across studies: ongoing pregnancy/live birth. Finally, those studies involving assisted reproduction were assessed for implantation rates.

Moderating variables were assessed for each study to determine impact upon outcomes. These included study type, control type (for treatment trials), whether or not the subjects had undergone earlier surgery, and study quality score (see Appendix 1 for scoring template). Study quality scores were calculated by two of the authors independently and the mean score used.

Analysis

After compilation into 2 × 2 table form for each study, the data were analyzed with Comprehensive Meta Analysis v.2

TABLE 1

The studies.

Study	Design	Control	Infertility treatment	Age (yrs), control vs. study	Location and no. of patients	Size (mm)	No. of fibroids per patient	Myomectomy trial	Uterine cavity evaluation[b]	Uniform evaluation of subjects	Inclusion and exclusion criteria specified	Single subject per outcome specified	Outcome assessment methodology specified
Stovall (15)	P	Infertile women without fibroids	IVF	35.9 vs. 35.8	SS 5, IM 86	Mean 24.2	1.8	No	HSG	No	Yes	No	No
Eldar-Geva (16)	R	Infertile women without fibroids	IVF/ICSI	35.5 vs. 35.7	SS 41, IM 55, SM 10	Means SS 24, IM 23.7, IC 44.8	SS 1.3, IM 1.8, IC 2.7	No	Not stated	No	No	No	Yes
Farhi (4)	R	Infertile women with tubal factor and without fibroids	IVF	33.5 vs. 34	SS/IM 28, SM 18	Not stated	Not stated	No	US	No	No	No	No
Narayan (5)	P	Infertile women without fibroids	IVF/none	34.5 vs. 36.6	SM 28	Not stated	Not stated	Yes	US	No	No	No	No
Varasteh (6)	R	Infertile women without fibroids	All treatments	37.2 vs. 35.2	SM 36	Not stated	Not stated	Yes	Hysteroscopy	No	Yes	Yes	No
Surrey 2001 (7)	R	Infertile women without fibroids	IVF/ICSI	36–42 vs. 37–43	IM 73 cycles	Mean 2.33	Not Stated	No	Hysteroscopy	Yes	Yes	No	Yes
Seoud (14)	R	Infertile women without fibroids and those with in situ fibroids	IVF	36.1 vs. 37.1	SS 10, IM 1	Myomectomy mean 89, myoma mean 31	Not stated	Yes	HSG	No	No	No	No
Ramzy (17)	R	Infertile women without fibroids	IVF/ICSI	34.7 vs. 34.0	SS 32, IM 12	SS mean 38, IM mean 32	1.2	No	US	No	No	No	No
Bulletti 1999 (13)	R	Infertile women without fibroids and those with in situ fibroids	None	Not done	SS/IM/SM 106	Not stated	Not stated	Yes	US	No	No	Yes	Yes
Bernard (9)	R	Infertile women without fibroids	None	35.7 vs. 34.5	IM 16	Range 10–50	1.4	No	Hysteroscopy	Yes	Yes	Yes	No
Dietterich (10)	R	Oocyte and embryo donor recipients without fibroids	Oocyte and embryo donor recipients	Recipient age 44.1 vs. 41.5	IM/SS 9	Range 6–26	1–6	No	US	No	Yes	Yes	Yes
Wang 2001 (18)	P	Infertile women without fibroids	None	32.7 vs. 35.5[a]	SS 13, IM 13, SM 8	Not stated	Not stated	No	US	No	Yes	No	Yes
Wang 2004 (19)	P	Oocyte donation recipients without fibroids	Oocyte donor recipients	Recipient age 39.5 vs. 43[a]	SS/IM 49	30.3 or less	Not stated	No	US	No	Yes	Yes	Yes
Check (22)	P	Infertile women without fibroids	IVF/ICSI	36.6 vs. 36.6	SS/IM 61	Range 6–51	1–7	No	HSG	No	Yes	Yes	Yes
Ng (20)	P	Infertile women without fibroids	IVF/ICSI	35 vs. 37[a]	SS/IM 77	Range 10–60	1–6	No	US	No	Yes	Yes	Yes
Hart (11)	P	Infertile women without fibroids	IVF/ICSI	34.6 vs. 36.4[a]	IM 112	Range 50 or less	1–4	No	US	No	Yes	Yes	No
Oliveira (23)	R	Infertile women without fibroids	ICSI	35.1 vs. 35.1	SS 82, IM 130, SS/IM 33	Range 4–69	1–4	No	HSG	No	Yes	Yes	No
Yarali (24)	R	Infertile women without fibroids	ICSI	35.6 vs. 36.0	SS 35, IM 73	Range 5–100	1–8	No	HSG	No	Yes	Yes	Yes
Bulletti 2004 (12)	P	In situ fibroids	IVF/ICSI	Not stated	SS/IM 84	At least one >50	1–5	Yes	US	Yes	Yes	Yes	No
Gianaroli (21)	R	Infertile women without fibroids	IVF/ICSI	35.7 vs. 35.8	IM/SM 75	19–48	1–7	No	US	No	No	No	Yes
Surrey 2005 (8)	R	Infertile women without fibroids and oocyte donor recipients without fibroids	IVF/ICSI and oocyte donor recipients	37.8 vs. 38.0, 41.3 vs. 40.0	IM/SS 55, SM 46	14–68	1–4	Yes	Hysteroscopy	No	Yes	No	Yes
Klatsky (25)	R	Infertile women without fibroids	Oocyte donor recipients	Donor age 26.2 vs. 24.7	IM/SS 94	Unknown range, mean 28 mm	Not stated	No	HSG	No	Yes	Yes	Yes
Casini (3)	RCT	In situ fibroids	None	Not compared, all less than 35	SM 94, IM 76	Unknown range	Not stated	Yes	HSG	Yes	Yes	Yes	Yes

Note: HSG = hysterosalpingography; ICSI = intracytoplasmic sperm injection; IM = intramural myoma; IVF = in vitro fertilization; P = prospective; R = retrospective; RCT = randomized control trial; SHG = sonohysterography; SM = submucous myoma; SS = subserosal myoma; US ultrasound.

[a] Statistically significantly older patients in the different groups.

[b] Indicated the highest quality investigative tool used in all study subjects.

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(Biostat, Englewood, NJ). Effects were reported as risk ratios, although odds ratios and log odds ratios were also calculated and in some cases used for analysis. The 95% confidence intervals were used to determine statistical significance, although given the number of outcomes this may be overly liberal. Homogeneity of trials included in all meta-analyses was tested using the Cochran Q test (26). Because heterogeneity was apparent in all analyses, the random effects model was used (27). This has the effect of giving less weight to larger studies than the fixed effect model, but it is more appropriate for the degree of heterogeneity encountered here.

Due to the heterogeneity, a meta-regression was performed to assess the degree of heterogeneity attributable to study design, analysis, and reporting (28). The mixed-effects regression technique (unrestricted maximum likelihood) was used, with study quality score as the predictor (independent) variable and log odds ratio as the response (dependent) variable.

Publication bias was explored by funnel plot. The existence of a significant publication bias and the "file drawer effect" (the lack of submission or acceptance of small negative-outcome studies) was calculated by the Begg and Mazumdar rank correlation test (29). If significant, the Duval and Tweedie trim and fill method was used to estimate the number of missing studies (30), and the Rosenthal classic fail-safe N method was used to determine the number of negative studies required to nullify the apparent effect (31).

RESULTS

Effect of Fibroids

When evaluating the outcomes of women with any location of fibroid, the relative risks of clinical pregnancy, implantation, and ongoing pregnancy/live birth were all significantly lower in women with myomas than in control subjects. In addition, the spontaneous abortion rate was significantly greater in women with fibroids. No significant difference in preterm delivery rates was observed (Table 2).

Given the effect of fibroids in aggregate, it appeared advisable to evaluate the effects of fertility by location. Data were initially broken down by SM location or "other," the former representing all women with intracavitary distortion and the latter representing women with fibroids that did not distort the cavity. The women with SM fibroids, compared with infertile women without fibroids, demonstrated a significantly lower clinical pregnancy rate, implantation rate, and ongoing pregnancy/live birth rate and a significantly higher spontaneous abortion rate. No difference was seen in rate of preterm delivery (Table 3). Women with no cavitary involvement had a significantly decreased implantation rate and ongoing pregnancy/live birth rate as well as an increased spontaneous abortion rate compared with nonfibroid control subjects. No significance was seen in clinical pregnancy rates or preterm delivery rates (Table 4).

Thus, SM fibroids seem to lower fertility, but this was also seen in fibroids not distorting the cavity. It seemed advisable to then evaluate nondistorting fibroids by location for their effect upon fertility.

When women with SS fibroids were examined in comparison with women without fibroids, no difference was observed for any outcome measure. In contrast, women with IM fibroids produced significantly lower clinical pregnancy rates, implantation rates, and ongoing pregnancy/live birth rates and significantly higher spontaneous abortion rates. No difference was seen in the rate of preterm delivery (Table 5A). When the analysis is restricted to prospective studies, only the clinical pregnancy rate loses statistical significance; all other effects remain unchanged (Table 5B). When the analysis is limited to those studies using a high-quality method to assess the uterine cavity in all subjects, only implantation rate maintains statistical significance (Table 5C). No changes in results are seen by elimination of studies involving subjects with earlier surgery or restricting inclusion to assisted reproduction studies.

Most investigators did not include size of fibroids as a variable when data analysis was performed. Five investigators did, however, report fibroid size and stratified their analysis accordingly. Categoric thresholds were 2, 3, 4, 5, and 6 cm. None of these studies found any significant difference in fertility outcomes compared with groups of infertile women without myomas, nor were there any statistical trends (5, 12, 13, 22, 23).

TABLE 2

Effect of fibroids on fertility: all locations.

Outcome	Number of studies/substudies	Relative risk	95% confidence interval	Significance
Clinical pregnancy rate	18	0.849	0.734–0.983	$P=.029$
Implantation rate	14	0.821	0.722–0.932	$P=.002$
Ongoing pregnancy/live birth rate	17	0.697	0.589–0.826	$P<.001$
Spontaneous abortion rate	18	1.678	1.373–2.051	$P<.001$
Preterm delivery rate	3	1.357	0.607–3.036	Not significant

Pritts. Fibroids and infertility. Fertil Steril 2009.

TABLE 3

Effect of fibroids on fertility: submucous fibroids.

Outcome	Number of studies/ substudies	Relative risk	95% confidence interval	Significance
Clinical pregnancy rate	4	0.363	0.179–0.737	$P=.005$
Implantation rate	2	0.283	0.123–0.649	$P=.003$
Ongoing pregnancy/live birth rate	2	0.318	0.119–0.850	$P<.001$
Spontaneous abortion rate	2	1.678	1.373–2.051	$P=.022$
Preterm delivery rate	0	—	—	—

Pritts. Fibroids and infertility. Fertil Steril 2009.

Effect of Myomectomy

As mentioned in Materials and Methods, two types of trials exist: those controlling with women having fibroids in situ, and those using infertile nonfibroid subjects as control subjects.

If fibroid removal is beneficial, myomectomy subjects would be expected to have higher pregnancy rates and lower abortion rates than those with fibroids in place. In those with SM fibroids, clinical pregnancy rate is indeed higher in the myomectomy group, but the ongoing pregnancy/live birth rate fails to reach statistical significance. The spontaneous abortion rate appears unchanged (Table 6). In women with IM fibroids, no significant differences are seen (Table 7). In both cases, studies are sparse.

When the control group is infertile women with no fibroids, myomectomy might be expected (if beneficial) to normalize the rates compared with controls. This is in fact seen with women having SM myomas: Clinical pregnancy rate, ongoing pregnancy/live birth rate, and spontaneous abortion rate are all statistically similar to control subjects (Table 6). No studies examined subjects with IM fibroids in this manner.

Metaregression

The range of study quality scores was 4–15.5. Despite this range, study quality did not prove to be a significant factor in study heterogeneity for any of the included meta-analyses, with *P* values of the slope ranging from .10 to .95.

Publication Bias

Among all the significant results obtained in these meta-analyses, only one demonstrated a significant rank correlation test (no treatment, all locations, ongoing pregnancy/live birth rate: two-tailed Kendall tau = 0.023). Missing study estimates ranged from 0 to 6, and the number of missing studies required to lose significance ranged from 3 to 144. In no case did the estimated number of missing studies equal or exceed the number required to reverse the conclusion.

DISCUSSION

The question of when to advise removal of a fibroid in the infertile female is a frequent clinical dilemma, but making conclusions based upon the available literature has been problematic. For many years clinical judgement was substituted for data; when studies were finally available, their quality was often so poor as to merely confound the issues further. In 2001, we attempted to make some sense of the existing literature by performing a systematic review and meta-analysis of several key issues (1). Unfortunately, we discovered not only a shortage of controlled trials, but also an even greater shortage of well constructed prospective investigations or randomized clinical trials. Now, 7 years later, the quality of the available literature has modestly improved.

Since publication of our manuscript in 2001, a type of consensus has emerged for several issues. It has become widely assumed that SS fibroids do not affect fertility or spontaneous

TABLE 4

Effect of fibroids on fertility: no intracavitary involvement.

Outcome	Number of studies/ substudies	Relative risk	95% confidence interval	Significance
Clinical pregnancy rate	24	0.897	0.800–1.004	Not significant
Implantation rate	14	0.792	0.696–0.901	$P<.001$
Ongoing pregnancy/live birth rate	16	0.780	0.690–0.883	$P<.001$
Spontaneous abortion rate	16	1.891	1.473–2.428	$P<.001$
Preterm delivery rate	2	2.767	0.797–9.608	Not significant

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TABLE 5

Effect of fibroids on fertility: intramural fibroids.

Outcome	Number of studies/ substudies	Relative risk	95% confidence interval	Significance
A. All studies				
Clinical pregnancy rate	12	0.810	0.696–0.941	$P=.006$
Implantation rate	7	0.684	0.587–0.796	$P<.001$
Ongoing pregnancy/live birth rate	8	0.703	0.583–0.848	$P<.001$
Spontaneous abortion rate	8	1.747	1.226–2.489	$P=.002$
Preterm delivery rate	1	6.000	0.309–116.606	Not significant
B. Prospective studies				
Clinical pregnancy rate	3	0.708	0.437–1.146	Not significant
Implantation rate	2	0.552	0.391–0.781	$P=.001$
Ongoing pregnancy/live birth rate	2	0.465	0.291–0.744	$P=.019$
Spontaneous abortion rate	2	2.384	1.110–5.122	$P=.002$
Preterm delivery rate	0	—	—	—
C. Studies using hysteroscopy in all subjects				
Clinical pregnancy rate	2	0.845	0.666–1.071	Not significant
Implantation rate	1	0.714	0.547–0.931	$P=0.013$
Ongoing pregnancy/live birth rate	2	0.733	0.383–1.405	Not significant
Spontaneous abortion rate	2	1.215	0.391–3.774	Not significant
Preterm delivery rate	1	6.000	0.309–116.606	Not significant

Pritts. Fibroids and infertility. Fertil Steril 2009.

abortion; in fact, very few investigators have bothered to look at this question. Similarly, it is agreed that SM myomas lower fertility rates and that their removal enhances rates of conception and live births. Both opinions have been reinforced by the present systematic review.

The largest remaining issue, however, is the importance of IM myomas. In 2001 we could find no evidence that IM myomas, in the absence of intracavitary distortion, would affect fertility. However, that conclusion changes with the present reanalysis. With the results of newer, often better, studies, it now appears that IM myomas may cause a detrimental effect on conceiving and reaching viability with a pregnancy. However, this is tempered by the poor evaluation of the uterine cavity in most such studies.

Even if IM fibroids do indeed decrease fertility (and this is far from conclusive), it is not a given that their removal will reverse the process and normalize fertility or even be beneficial to the patient. There are several excellent reasons for

TABLE 6

Effect of myomectomy on fertility: submucosal fibroids.

Outcome	Number of studies/ substudies	Relative risk	95% confidence interval	Significance
A. Controls: fibroids in situ (no myomectomy)				
Clinical pregnancy rate	2	2.034	1.081–3.826	$P=.028$
Implantation rate	0	—	—	—
Ongoing pregnancy/live birth rate	1	2.654	0.920–7.658	Not significant
Spontaneous abortion rate	1	0.771	0.359–1.658	Not significant
Preterm delivery rate	0	—	—	—
B. Controls: infertile women with no fibroids				
Clinical pregnancy rate	2	1.545	0.998–2.391	Not significant
Implantation rate	2	1.116	0.906–1.373	Not significant
Ongoing pregnancy/live birth rate	3	1.128	0.959–1.326	Not significant
Spontaneous abortion rate	2	1.241	0.475–3.242	Not significant
Preterm delivery rate	0	—	—	—

Pritts. Fibroids and infertility. Fertil Steril 2009.

TABLE 7

Effect of myomectomy on fertility: intramural fibroids (fibroids in situ controls).

Outcome	Number of studies/ substudies	Relative risk	95% confidence interval	Significance
Clinical pregnancy rate	2	3.765	0.470–30.136	Not significant
Implantation rate	0	—	—	—
Ongoing pregnancy/live birth rate	1	1.671	0.750–3.723	Not significant
Spontaneous abortion rate	1	0.758	0.296–1.943	Not significant
Preterm delivery rate	0	—	—	—

Pritts. Fibroids and infertility. Fertil Steril 2009.

avoiding myomectomy in the infertile woman with IM myomas. Abdominal or laparoscopic myomectomy can be associated with significant morbidity, including infection, damage to internal organs, and risk of blood or blood product transfusions. Also of concern for the infertile woman is the high rate of postoperative adhesion formation, especially with myomectomies performed through posterior uterine incisions (32–34). Add to these the risks of uterine rupture during pregnancy and increased likelihood of cesarean section, and there are many reasons to be wary of myomectomy when the indications are unclear.

As the present results show, there is no clear evidence at this time that myomectomy for IM fibroids is beneficial to fertility, despite the presence of a randomized clinical trial (3). However, given the magnitude of the risk ratio and the small number of studies and participants, it certainly deserves much further study. It would appear that investigation of removal of IM fibroids would head the priority list of issues for contemporary clinical myoma research. Ancillary issues in need of being addressed are the number of IM fibroids that necessitate removal, the size of IM fibroids that affect fertility, and whether or not proximity to the endometrium or even location within the uterus are of clinical importance. Hopefully, these will be topics carefully and thoroughly addressed by future investigators.

To appropriately address these issues in the future, methodologic concerns must be dealt with in a serious prospective manner. Patient age is an important confounder for any study where fertility rates are the measured outcome. Many of the manuscripts included in the present review fail to adjust for any disparity in ages between the women with myomas and the control subjects. This is important, because the ages of women with myomas is frequently greater than the control subjects, a bias that would be expected to decrease the pregnancy and delivery rates and increase the spontaneous abortion rates in women with fibroids.

Most published studies performed inadequate evaluation of fibroid location within the uterus. The most common shortcoming was the exclusive use of hysterosalpingograms or transvaginal ultrasonography to evaluate the uterine cavity. Hysterosalpingograms may have sensitivities as low as 50% and positive predictive values as low as 28.6% for intrauterine lesions (35). In a separate study evaluating infertile women, a specificity of 20% was reported compared with hysteroscopic findings (36). Therefore, if evaluation of the uterine cavity is limited to hysterosalpingography, imprecise fibroid localization is highly likely.

Transvaginal ultrasound was once thought to be an accurate tool for diagnosis of SM fibroids, with initial studies showing a sensitivity and specificity of 100% and 94%, respectively, and positive and negative predictive values of 81% and 100%, respectively, compared with hysteroscopy as the "gold standard" (37). However, current studies fail to show this high level of accuracy, with sensitivities as low as 69% and positive predictive values as low as 47% (38–44).

Sonohysterogram, hysteroscopy, and magnetic resonance imaging (MRI) are clearly the best techniques available to diagnose the presence of an intracavitary or SM fibroid. In 1993, Fukuda et al. (45) found that when evaluating IM or SM fibroids, sonohysterogram misdiagnosed only 1 of 22 of these myomas. In a second study, sonohysterography and hysteroscopy had sensitivity, specificity, and predictive values of 100% (46). Dueholm et al. studied preoperative vaginal sonography, sonohysterography, hysteroscopy, and MRI in 106 women scheduled for hysterectomy, with the findings compared with pathologic examination; MRI proved to perform the best, with 100% sensitivity and 91% specificity (44).

Sonohysterography or hysteroscopy were used to diagnose the submucosal or intracavitary location of fibroids for all study patients in only four of the controlled studies entered into the present analysis, and none used MRI. This likely led to under-reporting of intracavitary involvement in the other studies. This limitation may produce an apparent decrease in fertility rates for presumed IM myomas, when in fact an SM component is present and contributing to lower success rates. If the fibroids classified as IM truly do have an intracavitary component, then the true effect of SM myomas on fertility may have been underestimated and that of IM fibroids overestimated.

In addition to these issues, future studies should strive to more accurately classify IM fibroids. It is known that the

junctional zone of myometrium is ontogenetically, structurally, and hormonally different from outer myometrium. Magnetic resonance imaging can successfully distinguish junctional zone myometrium and outer myometrium; determining the precise location of IM fibroids might further define their impact upon fertility. Moreover, associated diseases, such as endometrial polyps, adenomyosis, and endometriosis, should be identified to determine if the fibroid effect is altered in the absence of such confounders.

With reviews of this nature, it is always possible that the preponderance of poor-quality studies overwhelms and obfuscates the resulting conclusions of high-quality trials. This does not seem to be the case here, because meta-regression demonstrated study quality scores to not significantly affect the observed effect in the meta-analyses. Furthermore, subanalysis limited to the best studies produced nearly identical results. There is also the potential danger of publication bias due to the lack of submission or acceptance of negative outcome trials, the so-called "file drawer" effect. That also seems to not be in play here, because few studies are estimated to be missing and their number is far fewer than the number needed to alter conclusions.

In summary, infertility patients with fibroids that impinge upon the endometrial cavity have poorer reproductive outcomes than those infertile patients without fibroids. In addition, those with IM myomas also may have a poorer reproductive outcome, but the lack of quality evaluations make this conclusion tenuous at best. Subserosal fibroids, however, seem to generate no obvious fertility issues. Removal of fibroids with an intracavitary component seems to be of benefit. There are as yet no data to support myomectomy in the treatment of IM myomas to improve fertility outcomes. The IM myoma should be the focus of future investigation, with particular emphasis on the performance of high-quality studies that carefully assess size, number, and proximity to the endometrium based on accurate cavity evaluation.

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STUDY QUALITY SCORING INSTRUMENT

What is the study design?

a. Randomized clinical trial—4 points
b. Prospective matched or cohort—2 points
c. Retrospective matched or cohort—1 point
d. Other—0 points

If prospective or randomized, how many subjects were lost to follow up?

a. Less than 10%—2 points
b. 10%–20%—1 point
c. Greater than 20%, unknown, or retrospective—0 points

How was the uterine cavity evaluated (must be for all patients)?

a. Hysteroscopy/sonohysterography—3 points
b. Hysterosalpingography—2 points
c. Ultrasound only—1 points
d. No assessment or not stated—0 points

How uniform was the evaluation of the subjects?

a. All subjects underwent a uniform evaluation—2 points
b. Evaluation was variable or not stated—0 points

Were the inclusion/exclusion criteria clearly specified?

a. Yes—2 points
b. No—0 points

What was the unit of time for outcome assessment?

a. Uniform for all subjects—2 points
b. Variable—0 points

Was the outcome assessment methodology clearly specified?

a. Yes—1 point
b. No—0 points

Was each subject included only once for each outcome?

a. Yes—2 points
b. No or unknown—0 points