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When Should Uterine Fibroids Be Treated?

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Abstract Fibroids are a common disorder of women, but in general, are best left untreated unless they are significantly symptomatic or an imminent health hazard. When treatment is needed, surgery remains the gold standard. For fertility, fibroids that impinge upon the uterine cavity should be removed to increase future pregnancy rates. There is no evidence that myomectomy for intramural fibroids, even those as large as 6 cm, increases fertility potential, or improves pregnancy outcome. Prophylactic myomectomy of large fibroids (largest diameter>5 cm) to decrease delivery complications is not recommended because it confers worse outcomes at delivery versus women with these large fibroids in situ. Medical treatment is transient, with most fibroids returning to pretreatment size a few months after treatment is stopped. It may, however, have a place for pretreating women before surgical removal, to treat anemia, or in perimenopausal women. Invasive radiological treatments (eg, uterine artery embolization and magnetic resonance guided ultrasound surgery) are effective for treating fibroids, but must be evaluated further before they can be recommended for women interested in future fertility.

Keywords Fibroids · Reproduction · Pregnancy · Fertility · Delivery · Miscarriage · Leiomyomata · Medical treatment · Hysterectomy · Surgery · Myomectomy · Uterine artery embolization · Gonadotrophin-releasing hormone agonists · Aromatase inhibitors · Infertility · Radiology

Introduction

Uterine fibroids, also know as leiomyomata, are a common disorder of reproductive-age women. They occur in up to 70% of Caucasians and 80% of African American women [1]. Their etiology is currently unknown, but it is believed that genetics, growth and angiogenic factors, and steroid hormones all play a role in the formation and subsequent growth of fibroids [2].

In women with fibroids, symptoms include infertility, miscarriage, delivery complications, menometrorrhagia, pelvic pain, bulk symptoms such as constipation and urinary frequency, and rare sequelae such as hemorrhage or hydronephrosis.

Because fibroids are so common in women, it is almost a disservice to call leiomyomata a pathologic entity. In several studies, women with minimal or no symptoms had no change in quality of life or symptomatology when no treatment was undertaken; thus, prophylactic treatment is unwarranted [3, 4].

There are a variety of circumstances, however, where intervention is potentially desirable. These circumstances will be discussed.

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Treatment Modalities

Physical Interventions

Hysterectomy is the most traditional surgical treatment of fibroids; it is both immediate and curative. It can be performed abdominally (vertical midline or Pfannenstiel incision), laparoscopically, vaginally, or as a combined procedure such as a laparoscopically assisted vaginal hysterectomy. Risks of these procedures include the standard risks of bleeding, infection, damage to organs (such as bowel, bladder, or ureter), and postoperative adhesions, which potentially lead to pain or distortion of normal pelvic anatomy.

In more recent years, supracervical hysterectomy has been added as an option, with removal of only the uterine body itself, leaving behind the cervical stump. Although initially purported to have benefits over a complete hysterectomy, this is not supported by the evidence. There are no differences in

sexual function or bladder function, and no differences in peri- or postoperative outcomes compared with standard hysterectomy. The supracervical hysterectomy may have postoperative risk of continued vaginal bleeding in as many as 25% of women [5]. This procedure is limited to women with no known cervical pathology, and if ultimate removal of the cervical stump is necessary, the surgery can be complicated, with increased risks for the patient [6].

Myomectomy is also an option, with removal of the fibroids themselves while leaving the uterus otherwise intact. This can be performed abdominally (vertical midline or Pfannenstiel incision), laparoscopically, vaginally, or laparoscopically assisted. The risks associated with this procedure are similar to other abdominal surgical procedures. It can also be performed hysteroscopically. One of the drawbacks to these procedures is the potential recurrence of fibroids with the need for further treatment. It is essential that patients undergoing myomectomy understand the potential for blood transfusion. For women likely to refuse such treatments due to religious or ethical issues, this may not be a viable option.

Myolysis is a technique in which a fibroid is either heated (thermal myolysis) or cooled (cryomyolysis) to such a degree that it is no longer viable, and a reduction in volume is seen. The procedure is usually performed laparoscopically, during which time a probe (bipolar, monopolar, laser, or metal with a circulating coolant) is inserted into the fibroid to affect destruction. This procedure is a minimally invasive option in reducing myoma volume [7].

Radiofrequency ablation is another minimally invasive alternative that relies on destruction of the myoma tissue. It entails either ultrasound or laparoscopic-guided insertion of a needle electrode into the myoma and uses heat energy to produce cell death and tissue necrosis. Preliminary data have been encouraging, with significant diminution in fibroid size seen as early as 3 months after treatment [8].

Magnetic resonance–guided focused ultrasound surgery (MRgUS) was first introduced in 2000, and approved by the US Food and Drug Administration in 2004. It is an interventional radiologic technique whereby high-energy focused ultrasound waves are utilized in a pulsatile function to heat and destroy the fibroid. Each high-frequency acoustic pulse reaches temperatures between 65°C and 85°C to produce coagulative necrosis of the fibroid, while sparing the surrounding myometrial tissue. This treatment has the advantage of pre- and post-procedure thermal mapping by magnetic resonance imaging to assess efficacy and safety of the ablative technique. Early data show it to be a safe and effective treatment modality [9].

There are limitations to which women can be treated; they must be less than 250 pounds, have a total uterine size less than 24 weeks, and have normal hemoglobin levels.

This novel treatment has limited data to assess treatment outcomes, but in a preliminary observational study there was an 85%–95% improvement in urinary symptoms, pain, and bleeding at 12 months post-procedure [10]. Thus far, 11% of women undergoing the procedure have required a second procedure within 2 years [11].

Uterine artery ligation is a minimally invasive option that addresses the uterine vasculature in treating the fibroid. It is performed either abdominally with ligation and permanent vascular occlusion, or vaginally for temporary vascular occlusion. This new technique has been performed in a limited fashion [12, 13]. It has a benefit of acting to occlude the uterine vessels and producing tumor ischemia, resulting in shrinkage of the fibroids, similar to some of the noninvasive treatments below, without the introduction of foreign bodies into the vasculature. There is, however, the real risk of ureteral damage with occlusion of these vessels via the vaginal approach. More data are needed before sound recommendations can be made.

Uterine artery embolization (UAE) is an interventional radiological treatment of fibroids with excellent outcomes. To perform this procedure, a catheter is introduced into the femoral artery, and then advanced to the distal portion of the uterine artery. Once this destination is reached, an embolizing agent is introduced. This is performed bilaterally. The result is irreversible ischemic damage to the fibroid. Normal myometrium, however, is protected due to extensive collateral circulation not available to the fibroids [14]. In an early meta-analysis of three randomized controlled trials with 234 women in 2006, 30%–46% reduction in myoma volume was seen with a decreased hospital stay and resumption of normal activities much sooner when compared with more invasive surgical techniques such as hysterectomy or myomectomy. These women were followed for 6 months postintervention [15].

Two more randomized controlled trials have been published since that time; one involving 28 hospitals in the Netherlands that compared UAE to hysterectomy, and a second comparing UAE to a variety of surgical treatments of fibroids. These studies had a follow-up period of 2 years. In the first trial, there were no differences in bulk symptoms or pain between the two groups, with a mean decrease in uterine volume of 48% in those undergoing UAE [16]. In the second trial, quality of life was no different between groups in any of the six components of the Short-Form General Health Survey [17].

There are significant side effects associated with UAE, the most prominent being post-procedure pain. This results in most women being admitted overnight for pain control, and some degree of pain requiring oral narcotics for as long as a week. There is also the more rare complication associated with the immune response to necrotic tissue termed the postembolization syndrome. It includes transitory fever, pain, nausea, and fatigue.

Thus far, the risk of death from this procedure is 1 in 25,000, due to either infection or pulmonary embolism. This can be contrasted with the risk of death from elective hysterectomy at 1 in 1,500 [18].

Endometrial ablation is minimally invasive and can be performed in the operating room or even in the office setting with minimal anesthesia. The technique is to burn, freeze, or remove the endometrial lining. Bleeding symptoms may be reduced, but any other symptoms resulting from the myomas are likely to be unaffected [18].

Medical Interventions

Drug treatment of the patient with fibroids can be used to diminish or reverse the growth of the tumors and that of the surrounding aberrant vasculature. Medical intervention also can be used to directly treat symptoms created by the fibroid.

It is known that both estrogen and progesterone play a critical, interconnected role in the initiation and growth of uterine fibroids [19]. For this reason, sex-steroid hormone–modulating drugs have been investigated in the treatment of leiomyomata.

Oral contraceptives are usually the first-line drugs to treat symptoms associated with fibroids, despite a lack of evidence to support their use. They do not, however, decrease size of fibroids. Similar results are also seen with medroxyprogesterone acetate (oral or depot) and levonorgestrel-releasing intrauterine devices. These drugs, if effective in reducing the menorrhagia, can be utilized indefinitely in the reproductive-age woman if she is not interested in concurrent childbearing.

Gonadotrophin-releasing hormone agonists have also been utilized to decrease both fibroid size and allow recovery from the anemia associated with blood loss due to these tumors. However, after cessation of drug use, the fibroids return to pretreatment size very quickly. In addition, side effects of this medication make it a reasonable treatment option only in the short term or for perimenopausal women.

Selective progesterone receptor modulators are progesterone receptor ligands that exert agonist, antagonist, or mixed effects on various target tissues. They have been utilized in the short term to treat fibroids, but the untoward side effect of endometrial hyperplasia makes their use limited [20]. Selective estrogen receptor modulators also have been utilized, but data thus far show no decrease in size nor decrease in any symptoms associated with the fibroids. There is no evidence to suggest that these particular drugs would be useful [21].

Aromatase inhibitors have been utilized with some promising initial results in shrinkage of fibroids without some of the side effects of the above drugs. A pilot study showed that the use of anastrozole, 1 mg, daily for 3 months decreased fibroid tumor size by 55% [22]. In a recent randomized controlled trial, letrozole, 2.5 mg, was utilized for 3 months and compared with triptorelin monthly. At the end of 3 months, the decrease in fibroid size was similar for both groups [23], but the main side effect of hot flashes was not seen in women utilizing letrozole. Further evaluation is warranted, but this medical treatment is truly promising.

Newer drugs that are nonhormonal in nature are being developed. Further studies will clarify their usefulness in the treatment of uterine myomas. These treatments are of particular interest to women of childbearing age because the goal would be to create a treatment that would decrease fibroid growth without affecting normal ovulation. They would also need to be safe for use in pregnancy; not an easy achievement. These drugs include pirfenidone, halofuginone, bexarotene, tranilast, heparin and heparin analogues, interferon alpha, thiazolidinediones, vitamin E and analogues [24], and NSAIDs [25].

Disease-Specific Treatment

The data regarding best treatment of women with fibroids are continually in flux. As we further understand the physiology of fibroids, novel drug treatments evolve. As innovative technology is discovered and refined, new surgical and minimally invasive treatments evolve. Treatment regimens also vary based upon number of fibroids, size of fibroids, symptoms and the tolerance of those symptoms, age of the woman affected, and her desire for future reproduction.

In the past, in women with incessant uterine hemorrhage or hydronephrosis, hysterectomy was the gold standard. With the improved surgical skills of the gynecologist, myomectomies soon became a valid treatment option for these women. Currently, there are many treatment options for women with these symptoms, often times including a combination of drug treatment and more invasive treatment.

Infertility

Myomectomy is the most commonly employed procedure among those attempting to improve reproductive potential in women with fibroids. For value to be established, two questions must be answered in the affirmative:

(1) Do fibroids decrease reproductive success?
(2) Does their removal (myomectomy) improve outcomes?

Plausibility

Plausibility is a key component when attempting to demonstrate cause-and-effect relationships. Unfortunately, little experimental attention has been directed at the mechanisms by which fibroids may reduce fertility. Clearly, extensive distortion by large or multiple fibroids may alter the required juxtaposition of pelvic structures, impairing such key processes as ovum pickup by the Fallopian tube and sperm, ovum, and embryo transport by the tube. By distorting the uterine

cavity contour, mechanical pressure may adversely affect gametes and embryos. It has been suggested that uterine fibroids, by altering the normal pattern of uterine contractility, could inhibit proper gamete transport [26]. Tumors protruding into the uterine cavity may produce local inflammation, creating a hostile environment for gamete/embryo survival [27]. Fibroids also may alter blood flow, either mechanically or via biochemical influence, reducing the efficiency of the implantation process [28].

Thus, despite a paucity of experimental data, many plausible (but unproven) mechanisms have been proposed to explain an adverse effect of uterine fibroids upon fertility.

Issues with Existing Data: Heterogeneity of Disease

It is clear that fibroids can and do cause infertility and other reproductive problems in some women. However, the disease is quite heterogeneous. While it is a foregone conclusion that a highly distorted uterus with dozens of large- and medium-sized fibroids will have reproductive difficulty, it is equally likely that a woman with a single small, pedunculated subserosal myoma will suffer no ill effects. The difficulty for researchers and clinicians alike lies in the determination of which defining characteristics of the disease "uterine leiomyoma" contribute to reproductive problems, and to what degree each of these parameters is a factor.

Fibroid uteri differ in the number present, their size, their location, and their histology/biochemistry. To truly understand the impact of fibroids on reproduction, each of these factors should be evaluated carefully and analyzed for relative importance. Unfortunately, most existing studies have ignored size and number. Histology and biochemical activity currently can be studied only in surgical trials, and no such investigations exist at present.

The most commonly examined of the above factors is location. Fibroids may be present as subserosal, intramural, or submucosal, or a combination of these locales. As will be detailed, the ability to differentiate submucosal from intramural may be particularly critical. Yet, most published studies have an inadequate evaluation of fibroid location within the uterus. The most common shortcoming is 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 [29]. In a separate study evaluating infertile women, a specificity of 20% was reported when compared to hysteroscopic findings [30]. Thus, 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 submucous fibroids, with initial studies showing a sensitivity and specificity of 100% and 94%, respectively; positive predictive value of 81%; and negative predictive value of 100% when compared with hysteroscopy as the "gold standard" [31]. 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% [32–38].

Sonohysterogram, hysteroscopy, and magnetic resonance imaging (MRI) are clearly the best techniques available to diagnose the presence of an intracavitary or submucous fibroid. In 1993, Fukuda et al. [39] found that, when evaluating intramural or submucosal 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% [40]. Dueholm et al. [38] studied preoperative vaginal sonography, sonohysterography, hysteroscopy, and MRI in 106 women scheduled for hysterectomy, with the findings compared to pathologic examination. MRI proved to perform the best, with 100% sensitivity and 91% specificity.

In addition to the issues mentioned, the precise location within myometrium of intramural myomas may be relevant. It is known that the junctional zone of myometrium is ontogenetically, structurally, and hormonally different from outer myometrium. MRI can successfully distinguish junctional zone myometrium and outer myometrium, but other modalities cannot.

Issues with Existing Data: Confounding Factors

The difficulty in studying a pathology's effect upon reproduction lies in the relatively large number of additional factors that affect reproductive outcome. Carefully controlling for such factors is paramount, yet few studies actually perform the exclusions or statistical adjustments necessary to avoid confounding effects of such factors. Several, in particular, are worth mentioning.

Patient age is an important confounder for any study where fertility rates are the measured outcome. The age of women with myomas is frequently greater than that of the control patients, due to the increased likelihood of myoma formation with advancing age. This factor alone may be responsible for decreasing fertility, and should always be examined and adjusted for when necessary.

Also important are associated diseases known or believed to influence reproductive success. Thorough investigation and correction for such disorders as abnormal semen samples, endometrial polyps, Müllerian anomalies, endometriosis, and pelvic adhesions should ideally be performed; unfortunately, this has been all too infrequently done in existing studies.

The Data

The medical literature regarding this topic is somewhat confusing and contradictory. Multiple studies have been

performed to determine the effects of fibroids and their removal upon infertility, but many of the findings are disparate, with the vast majority of studies suffering from methodological flaws. The reports are often poorly designed, do not include control groups or utilize patients as their own historical controls, and confounding variables, such as patient age, are rarely corrected for in the statistical analysis. Frequently, conclusions by the authors are unsupported by the data.

In 2001 the first meta-analysis addressing fibroids and infertility was published [41]. In that initial analysis, only those studies in which there was a control group were included; three were prospective and eight retrospective. The data were analyzed for effect of any fibroid upon fertility as well as specific fibroid location. The analysis revealed that only those fibroids with an intracavitary component (submucosal fibroids) affected fertility outcomes, including lower pregnancy rates (RR 0.30; CI 0.13–0.70) and implantation rates (RR 0.28; CI 0.10–0.72).

In the treatment trials, when submucosal fibroids were removed, there were increased pregnancy rates compared with infertile controls patients with fibroids left in place (RR 1.72; CI 1.13–2.58) and delivery rates were comparable to infertile women that did not have fibroids (RR 0.98; CI 0.45–2.41)

After our original review, there were seven more meta-analyses published, including an update from the original author [42•] through 2009. In the follow-up meta-analyses performed by us, again, only controlled or randomized controlled trials were included. By 2009, there were 23 studies that could be included, with nine prospective and one randomized. Of these studies, seven addressed treatment with myomectomy; however, in only four studies did the control groups comprise women with fibroids in situ.

There were again a myriad of problems with the studies, including age discrepancies between women with (older) and women without fibroids (younger), as well as with the modality in which fibroid location was identified. In only a few studies were the fibroid locations diagnosed with either sonohysterogram or hysteroscopy.

The results were similar to the data gleaned from the original meta-analysis. Again, there appeared to be no effect of subserosal fibroids upon fertility and decreased reproductive performance with submucosal fibroids. For women with submucosal fibroids, the clinical pregnancy rate was lower (RR 0.36, CI 0.18–0.74), the implantation rate was lower (RR 0.28, CI 0.12–0.65), the live birth rate was lower (RR 0.32, CI 0.12–0.85), and the spontaneous abortion rate was higher (relative risk 1.68, CI 1.37–2.05 [Table 1]).

Again, removal of submucosal fibroids conferred benefit for reproduction with an increase in clinical pregnancy rates (RR 2.03, CI 1.08–3.82), and when utilizing control groups of women with infertility and no submucosal fibroids, the fertility findings were now comparable (Table 2).

The most controversial area in previous analyses had been intramural fibroids, which have been shown to either decrease or not alter fertility depending upon how the review was conducted. In our recent meta-analysis intramural fibroids did indeed impact clinical pregnancy rate (RR 0.81, CI 0.70–0.94), implantation rate (RR 0.68, CI 0.59–0.80), ongoing pregnancy or live birth rate (RR 0.70, CI 0.58–0.85), and spontaneous abortion rate (RR 1.75, CI 1.23–2.49 [Table 3A]).

However, when only prospective studies were included, the differences in clinical pregnancy rates were no longer significantly decreased (RR 0.71, CI 0.44–1.15) for those women with intramural fibroids (Table 3B). In a further subset analysis, in which only those women with an adequate evaluation of the uterine cavity via hysteroscopy were included, the only differences that could be seen with intramural fibroids were implantation rates (RR 0.7, CI 0.55–0.93). The ongoing and live pregnancy rate and spontaneous abortion rate were no longer significantly different from control patients (RR 0.73, CI 0.38–1.4 and RR 1.22, CI 0.39–3.77, respectively [Table 3C]).

To confound the issue further, an excellent investigation was published after our last meta-analysis. This study showed that a single intramural fibroid was clearly not associated with infertility. In this study, a homogenous population with a single intramural fibroid had no intracavitary component as diagnosed by hysteroscopy, and a single diagnosis (male fertility) and treatment (intracytoplasmic sperm injection) for all those being evaluated [43••]. Implantation rates were identical in both groups, as were clinical pregnancy rates and miscarriage rates. The fibroids ranged in size from 5 to 43 mm.

Subsequent to our meta-analysis, another meta-analysis [44] was performed, this time including the study by Bozdag et al. [43••]. Findings were similar to those in our systematic review. Unfortunately, the authors did not perform any subset analyses extracting studies of higher quality.

Even if we suppose that intramural fibroids do decrease fertility, their removal would only be justified if myomectomy was shown to improve fertility rates. The available data addressing this issue comprise two surgical trials, one prospective study [45], and a single randomized trial [46]. Taken together, these studies failed to show an increase in clinical pregnancy rates (RR 3.77, CI 0.47–30.14), ongoing pregnancy or live birth rates (RR 1.67, CI 0.75–3.72), or spontaneous abortion rates (RR 0.76, CI 0.30–1.94). Thus, in regards to fertility issues, there is no evidence to support myomectomy for intramural fibroids.

At present, there are no actual studies addressing the newer treatment modalities and fertility issues. Most studies simply report the outcomes after pregnancies have been achieved in women post-treatment. There is, however, some indirect evidence suggesting that UAE may be detrimental to future fertility due to two issues.

Table 1 Effect of fibroids on fertility: submucous fibroids

Outcome	Studies/substudies, *n*	Relative Risk	95% Confidence Interval	Significance
Clinical pregnancy	4	0.363	0.179–0.737	*P*=0.005
Implantation rate	2	0.283	0.123–0.649	*P*=0.003
Ongoing/live birth rate	2	0.318	0.119–0.850	*P*=0.001
Spontaneous abortion rate	2	1.678	1.373–2.051	*P*=0.022
Preterm delivery rate	0			

(*From* Pritts et al. [42•], *with permission*)

First is the question of effect of UAE upon the endometrial cavity. In an excellent study recently published comparing UAE to uterine artery ligation, a post-procedure hysteroscopy revealed that women who underwent an embolization had a startlingly high rate of cavity necrosis (59.5%). Those undergoing surgical ligation had a far lower rate (2.7%) [47].

Second is the issue of post-UAE ovarian reserve. Hehencamp et al. [48] looked at both pre- and post-UAE anti-Müllerian hormone and follicular-stimulating hormone levels and found a decrease in ovarian reserve in all women after the procedure was performed.

In summary, the best available evidence suggests submucous myomas are detrimental to fertility, and hysteroscopic myomectomy improves fecundity. Subserous myomas, in contrast, have not been shown to affect fertility.

The intramural fibroid still presents a clinical conundrum. It remains unclear as to whether these fibroids truly have an affect on fertility, with surgical trials yet to show a benefit to their removal. Clearly, this is the area where more investigation is needed. Areas of inquiry should include number of fibroids, size, and location within uterus. Higher-quality study designs will help us obtain meaningful data for more reliable answers. However, at this time, excision of intramural fibroids to increase reproductive potential is not recommended.

At this point, also, the data indirectly suggest that newer interventional radiological techniques may decrease overall fertility potential if used to treat fibroids preconception.

Pregnancy

In the past, expert (and biased) opinion was that fibroids would increase in size during pregnancy. This, however, does not seem to be the case. Up to 75% of fibroids will decrease in size from 20 weeks gestation until delivery, based upon ultrasonographic evidence [49].

The most common complaint with fibroids in pregnancy is pain [50]. Although this is a rare occurrence, the most effective treatment thus far has been NSAIDs. Of note, NSAID treatment should be restricted to the first and second trimester. If used in the third trimester, it may lead to fetal complications such as early closure of the fetal ductus arteriosis, pulmonary hypertension, decreased renal function, necrotizing enterocolitis, intracranial hemorrhage, oligohydramnios, and issues of maternal platelet function near delivery [51].

Delivery

Based upon several retrospective cohorts or case-controlled studies, there is an increased risk of complications at delivery including Caesarean section, malpresentation, labor dystocia, postpartum hemorrhage, peripartum hysterectomy, retained placenta, chorioamnionitis or endometritis, intrauterine growth retardation, preterm labor, preterm delivery, placenta previa, first trimester bleeding, placental abruption, preterm premature rupture of membranes or premature rupture of

Table 2 Effect of myomectomy on fertility: submucous myomas

Outcomes	Studies, *n*	Relative Risk	95% Confidence Interval	Significance
A. Controls: fibroids in situ *(no myomectomy)*				
Clinical regnancy rate	2	2.034	1.081–3.826	*P*=0.028
Implantation rate	0			
Ongoing pregnancy/live birth rate	1	2.654	0.920–7.658	NS
Spontaneous abortion rate	1	0.771	0.359–1.658	NS
Preterm delivery rate	0			
B. Controls: infertile women with no fibroids				
Clinical pregnancy rate	2	1.545	0.998–2.391	NS
Implantation rate	2	1.116	0.906–1.373	NS
Ongoing pregnancy/live birth rate	3	1.128	0.959–1.326	NS
Spontaneous abortion rate	2	1.241	0.475–3.242	NS
Preterm delivery rate	0			

NS not significant

(*From* Pritts et al. [42•], *with permission*)

Table 3 Effect of fibroids on fertility: intramural fibroids

Outcome	Studies, *n*	Relative Risk	95% Confidence Interval	Significance
A. All studies				
Clinical pregnancy rate	12	0.810	0.696–0.941	$P=0.006$
Implantation rate	7	0.684	0.587–0.796	$P<0.001$
Ongoing pregnancy/live birth rate	8	0.703	0.583–0.848	$P<0.001$
Spontaneous abortion rate	8	1.747	1.226–2.489	$P=0.002$
Preterm delivery rate	1	6.000	0.309–116.606	NS
B. Prospective studies				
Clinical pregnancy rate	3	0.708	0.437–1.146	NS
Implantation rate	2	0.552	0.391–0.781	$P=0.001$
Ongoing pregnancy/live birth rate	2	0.465	0.291–0.744	$P=0.019$
Spontaneous abortion rate	2	2.384	1.110–5.122	$P=0.002$
Preterm delivery rate	0			
C. Studies with hysteroscopy in all subjects				
Clinical pregnancy rate	2	0.845	0.666–1.071	NS
Implantation rate	1	0.714	0.547–0.931	$P=0.013$
Ongoing pregnancy/live birth rate	2	0.733	0.383–1.405	NS
Spontaneous abortion rate	2	1.215	0.391–3.774	NS
Preterm delivery rate	1	6.000	0.309–116.606	NS

NS not significant

(*From* Pritts et al. [42•], *with permission*)

membranes. The problems with these studies, however, is that they were too heterogenous to allow for meta-analyses to be performed, they were certainly underpowered to evaluate the outcomes of more rare occurrences, and the groups of women with fibroids were often times older than the control groups, leading to bias in the data [52].

Another flaw with the studies mentioned is that their control groups comprised women without fibroids. There are as yet no prospective studies addressing fibroid influence upon delivery with comparisons between those with fibroids in situ versus those status postmyomectomy.

Recently, a group from Japan addressed the issue from a surgical standpoint, albeit in a retrospective fashion [53••]. They looked at women who had myomectomies for large intramural fibroids (diagnosed as those with a mean diameter>5 cm) compared with those women who had the fibroids left in situ. The women were similar in age, gravidity and parity, and twin and placenta previa rates.

In this study, women with the myomectomy were more likely to undergo Caesarean section versus those with large intramural fibroids in situ (74% vs 32%, $P<0.001$), had more blood loss (500 vs 510 mL, $P=0.005$) and more preterm delivery (35% vs 15%, $P=0.002$). Their recommendation was to leave fibroids in situ, even if they were large intramural fibroids with largest mean diameters greater than 5 cm, because removal confers serious sequelae at delivery.

This is a very simple, yet elegant look at this very controversial topic. It is the first study addressing this issue, and prophylactic removal of intramural fibroids, particularly those greater than 5 cm, is not recommended to decrease delivery complications. On the contrary, it may increase complication rates.

Several groups have followed the pregnancies of their patients after conception status post-UAE. In following 24 pregnancies from the Ontario Multicenter trial, there was a 50% rate of Caesarean section and a 22% rate of preterm birth and small-for–gestation age infants, and abnormal placentation was found in 17% of women [54].

Goldberg and Pereira [54] looked at pregnancy outcomes in patients after UAE and laparoscopic myomectomy. In those undergoing UAE, there was increased risk of preterm delivery (OR 6.2, CI 1.4–27.7), and malpresentation (OR 4.3, CI 1.0–20.5). Based upon this information, women interested in future conception must be advised that there are risks associated with UAE that may be detrimental to their pregnancy and delivery [55].

In women undergoing magnetic resonance–guided focused ultrasound surgery, outcome data have been accumulated on 54 pregnancies. Of the term deliveries reached, 94% were vaginal. Compared with UAE, there were fewer stillbirths and low–birth weight infants. At this time, however, more data are needed before recommendations can be made for women interested in future childbearing [56].

Miscarriage

Spontaneous abortion is a relatively common phenomenon in pregnancy, but is a difficult issue to study consistently because the rate will change dramatically based upon the time of pregnancy diagnosis and the method of study inclusion. The

earlier the diagnosis of pregnancy is made, the higher the detected rate of spontaneous abortion will be. This becomes problematic in retrospective studies of pregnant patients because the time of pregnancy diagnosis is generally highly variable. An exception to this may be in women undergoing fertility treatment, particularly assisted reproduction, where pregnancy determination may be routinely performed at a uniform time in early gestation.

It is certainly plausible that myomas affect the rate of spontaneous abortion. Mechanisms suggested include abnormal placentation, impaired blood flow, adverse mechanical effects, and biochemical impairment of the developing pregnancy.

One meta-analysis that is limited to controlled studies investigating infertile women attempting to conceive has been published [42•]. These data clearly demonstrated an increased risk of spontaneous abortion in women with fibroids versus control patients with no myomas. Furthermore, when analyzed by fibroid location, an increase in abortion rate was seen in women with submucous myomas and intramural myomas; subserosal fibroids did not appear to increase the spontaneous abortion rate (Table 4).

In addition to the studies included in the meta-analysis above, three additional studies can be considered. One, published subsequent to the above meta-analysis [42•], is limited to women with intramural myomas [43••]. Two early studies chose to investigate women seen in the first trimester for ultrasonographic examination; design shortcomings include inconsistency in time of pregnancy diagnosis and an inherent bias in which patients were referred for ultrasound examination [57, 58]. Nevertheless, inclusion of these three studies does not change the overall conclusion: uterine fibroids increase the rate of spontaneous abortion. When re-analysis by location is performed, the ten studies examining intramural fibroids and spontaneous abortion rate show a relative risk of 1.604 (95% CI, 1.207–2.131; $P=0.001$). In addition, the three trials examining subserosal fibroids and spontaneous abortion now show a significantly increased risk of 2.190 (95% CI, 1.221–3.930; $p=0.009$) [59].

Investigation of the relationship between fibroid number and spontaneous abortion rate suggests women with multiple (greater than two) myomas have a higher rate of miscarriage than those with none or one [57, 58]. Fibroid size has not been shown to affect spontaneous abortion rate [57].

There is also an excellent study comparing miscarriage rates after UAE versus abdominal myomectomy. In this randomized controlled trial, the interventions were completed and pregnancies were then followed ($n=50$). In women who had a myomectomy, the miscarriage rate was 23%. Conversely, in women that had the UAE, the miscarriage rate was 60% ($P<0.05$) [60].

In summary, it appears likely that fibroids increase the spontaneous abortion rate, and this may be true for all locations. The effect may be marginal with a single myoma, but appears to increase with fibroid number. Little data exist on the effect of myomectomy upon spontaneous abortion rate, and those few studies that do exist fail to show a benefit. Better treatment trials are definitely needed to determine if this failure to demonstrate benefit is an anomaly of the study designs and participant numbers or whether surgery really does not reverse the adverse effect of fibroids upon early pregnancy. The newer interventional radiological techniques seem to confer increased miscarriage rates, and should be undertaken with caution.

Conclusions

Uterine fibroids are common, and their mere existence does not necessitate treatment. In women with hemorrhage resistant to medical treatment, or bulk disease leading to dilation or obstruction of ureters, treatment should be undertaken. In women with infertility and intracavitary fibroids, there is a decrease in fertility and an increase in miscarriage rates. Submucosal myomectomy produces increased pregnancy rates. In women with intramural fibroids, implantation rates may be decreased, but removal of fibroids has not been shown to be of benefit. Subserosal fibroids have no effect upon fertility outcomes. While women with fibroids in pregnancy seem to have more complications than those without such tumors, there is no evidence that myomectomy improves outcomes. Existing medical treatment will render the woman infertile during the treatment phase. Those medical treatments that work on symptomatology, such as menorrhagia, without affecting the volume of fibroid can be used indefinitely. Those that work by reducing fibroid size are generally associated with significant side effects and thus are limited to preoperative or perimenopausal use.

Surgical therapy at present remains the mainstay of treatment of uterine fibroids. However, newer, less invasive

Table 4 Effect of fibroids on spontaneous abortion rate

Location	Studies/substudies, *n*	Relative Risk	95% Confidence Interval	Significance
All locations	18	1.678	1.373–2.051	$P<0.001$
Subserosal	2	1.197	0.465–3.086	NS
Intramural	8	1.747	1.226–2.489	$P=0.002$
Submucosal	2	1.678	1.373–2.051	$P=0.022$

NS not significant

(*From* Pritts et al. [42•], *with permission*)

radiological treatment modalities may change the future of fibroid treatment of women. As the evidence regarding optimum treatment of uterine leiomyomata improves, no doubt the available treatment modalities will be modified and expanded. It is important that practitioners rely not on dogma, but upon the best available evidence when deciding on treatments for their patients suffering from the untoward effects of fibroids.

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- • Of Importance
- •• Of major Importance

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