REPRODUCTIVE ENDOCRINOLOGY AND INFERTILITY

Fibroids and reproductive outcomes: a systematic literature review from conception to delivery

Peter C. Klatsky, MD; Nam D. Tran, MD, PhD; Aaron B. Caughey, MD, PhD; Victor Y. Fujimoto, MD

We examined the published relationship between uterine fibroids and reproductive outcomes. Submucosal fibroids had the strongest association with lower ongoing pregnancy rates, odds ratio, 0.5; 95% confidence interval, 0.3-0.8, primarily through decreased implantation. Cumulative pregnancy rates appeared slightly lower in patients with intramural fibroids 36.9% vs 41.1%, which may reflect biases in the literature; however, patients with intramural fibroids also experienced more miscarriages, 20.4% vs 12.9%. Adverse obstetric outcomes are rare and may reflect age or other differences in fibroid populations. Increased risk of malpresentation (odds ratio, 2.9; 2.6-3.2), cesarean (odds ratio, 3.7; 3.5-3.9), and preterm delivery (odds ratio, 1.5; 1.3-1.7) are reported; however, the incidence of labor dystocia was low (7.5%). There was no conclusive evidence that intramural or subserosal fibroids adversely affect fecundity. More prospective, controlled trials are needed to assess the effects of myomectomy. Good maternal and neonatal outcomes are expected in pregnancies with uterine fibroids.

Key words: fibroids, infertility, myomas, pregnancy

An estimated 20-40% of women will have uterine fibroids develop during their reproductive years.[1] African-American women are nearly 3 times as likely as white women to have fibroids develop, and age is the most common risk factor for fibroids among all women.[2] Nulliparity, a long history of cigarette smoking and a prolonged menstrual cycle have also been reported as risk factors in white women.[3] The number of pregnant women with fibroids ranges from a conservative estimate of 2.7% in women undergoing routine second-trimester pregnancy ultrasounds, 12.6% in women undergoing in vitro fertilization (IVF) treatment, and may exceed 25% in older women who undergo ovum donor recipient IVF.[4-6] The current trend of delaying childbearing, along with advances in our ability to prolong a woman's reproductive timeline, ensures that an increasing number of women with fibroids will present for infertility, prenatal, and obstetric care.

In recent years, a number of small- to medium-sized studies have reported infertility treatment and obstetric outcomes in patients with uterine fibroids. In this article, we reviewed the evidence regarding an association between fibroids and the continuum of various reproductive outcomes. We searched the PUBMED databases by using the terms, "fibroid," "leiomyoma," "infertility," "pregnancy," and "obstetric complications" and cross-referenced all relevant articles to find controlled studies comparing outcomes in women with and without fibroids. We evaluated each article and quantitatively summarized the findings of controlled studies.

From the Department of Obstetrics, Gynecology and Reproductive Science (Dr Klatsky), Mount Sinai School of Medicine New York, NY; and Department of Obstetrics, Gynecology, and Reproductive Sciences (Drs Tran, Caughey, and Fujimoto), University of California, San Francisco, San Francisco, CA.

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Fibroids and Infertility: Embryo Implantation

The association between fibroids and implantation remains controversial. Some authorities believe that fibroids have a detrimental effect on implantation, either through impaired transport of gametes, altered uterine contractility, or adverse effects on the endometrium.[7] None of these hypotheses have been proven and few have been rigorously tested.

The increased use of ultrasonography has resulted in the increased diagnosis of uterine fibroids in asymptomatic women with unexplained infertility. Some initial reports noted improved pregnancy rates in asymptomatic women with primary infertility and who underwent removal of their fibroids; however, most of these studies lacked adequate controls and none were randomized.[8] Unfortunately, in the absence of controls, such studies can establish the safety of myomectomy but do not support a therapeutic benefit for women with infertility.

Recently, researchers studied various controlled populations of patients undergoing IVF to assess the effect of fibroids on implantation. Multiple outcome variables, including implantation, ongoing pregnancy, and miscarriage rates, have been studied. Currently, most authorities give greater plausibility to the hypothesis that submucosal fibroids are associated with the greatest adverse effect on implantation and placentation. The role of intramural fibroids is more controversial. Subserosal and pedunculated fibroids, with greater than 50% of their mass outside the myometrial border are unlikely to cause adverse outcomes.[9]

Implantation-submucosal fibroids

A review of IVF outcomes that included 24 patients undergoing 86 cycles found a 70% decrease in pregnancy rate in women with submucosal fibroids com-

TABLE 1
Submucosal fibroids

	Study design; number of patients	Fibroid diameter: mean (range)	Implantation rate[a]		Clinical pregnancy rate[b]		Spontaneous abortion rate[c]	
			Fibroids	No fibroids	Fibroids	No fibroids	Fibroids	No fibroids
Farhi et al[7d]	Retrospective cohort. 18 IM fibroid patients, 50 controls	(<70 mm)	2.7% 5/179	9.8% 35/357	9.7% 5/55	25.2% 32/127	40% 2/5	25% 8/32
Eldar-Geva et al[9d]	Retrospective cohort. 6 study patients, 249 controls.	45 mm ± 26	4.3% 1/23	12.3% 94/763	10% 1/10	30.8% 98/318	0% 0/1	16.3% 16/98
Cassini et al[14] (SM)	Prospective, observational. Spontaneous conceptions, following timed intercourse.	(<40 mm)			21.4% 9/42	40.4% 21/52	55.6% 5/9	42.9% 9/21
Cumulative rates			3.0% 6/202 OR 0.39 (0.24-0.65)	11.5% 129/1120	14% 15/107 OR 0.44 (0.28-0.70)	30.4% 151/497	46.7% 7/15 OR: 3.85 (1.12-13.27)	21.9% 33/151

IM, intramuscular; *OR*, odds ratio; *SM*, submucosal.

[a] No. of sacs per no. of embryos transferred.

[b] No. of cycles with a gestational sac or living embryo per transfer.

[c] Clinical miscarriage after documented clinical pregnancy.

[d] Included repeat cycles in the same patient.

Klatsky. Fibroids and reproductive outcomes. Am J Obstet Gynecol 2008.

pared with infertile controls.[10] This decrease was attributable mostly to a 72% decrease in implantation rate. Most reproductive endocrinologists have since been recommending resection of submucosal fibroids, before proceeding with assisted reproductive technologies. Unfortunately, evidence supporting this recommendation remains limited to a small data set, which included a total of 24 patients. Table 1 summarizes the findings in controlled studies of women with submucosal fibroids. Although there are no randomized studies comparing patients with submucosal fibroids undergoing hysteroscopic resection to patients managed conservatively, the safety of hysteroscopic myomectomy has been well demonstrated. After hysteroscopic myomectomy, patients achieve pregnancy rates that are comparable with control groups without fibroids or prior hysteroscopic myomectomies.[11-13]

The routine resection of submucosal fibroids in patients with infertility was recently supported by a study comparing spontaneous pregnancy rates in women with at least 1 year of infertility and submucosal fibroids.[14] Of women who chose to undergo myomectomy, 40.4% were successful within 1 year of trying to conceive spontaneously, vs 21.4% in the cohort who declined myomectomy. It is possible that patients who were more aggressive about pursuing surgery were also more aggressive about intercourse timing and frequency, thus possibly increasing their chances to conceive spontaneously.

Despite the limitations of each study, several trends emerge in patients with submucosal fibroids, with decreases in implantation rates from 11.5% to 3.0% and in ongoing pregnancy rates from 30% to 14% (Table 1). Similarly, women with submucosal fibroids show a trend toward an increased risk of miscarriage from 22% to 47%.

Implantation: intramural fibroids

In contrast to the limited data on submucosal fibroids, many recent studies reported data for women with asymptomatic intramural fibroids presenting with infertility for IVF.[5-7,9,14-27] Unfortunately, results from these studies are inconsistent (Table 2).

In 1998, Elder-Geva et al[9] reported an adverse effect on ongoing pregnancy rates in patients with submucosal (n = 9) and intramural (n = 46) fibroids, but no difference was observed among patients with subserosal (n = 33) fibroids when compared with controls without fibroids. These findings contrast with those of a smaller study that found no difference in pregnancy rates when fibroids did not distort the endometrial cavity.[5] Multiple studies have since sought to investigate the association between intramural fibroids and implantation outcomes.

Hart et al[16] reported the largest prospective, controlled study to investigate the effect of small (less than 5 cm) intramural fibroids and found lower implantation and ongoing pregnancy rates in patients with fibroids compared with no fibroids (11.9% vs 20.2% and 15.1% vs

TABLE 2
Intramural fibroids: controlled studies

	Study design; number of patients	Fibroid diameter: mean (range)	Implantation rate[a]		Clinical pregnancy rate[b]		Spontaneous abortion rate[c]	
			Fibroids	No fibroids	Fibroids	No fibroids	Fibroids	No fibroids
Farhi et al[7d]	Retrospective cohort. 28 IM fibroid patients, 50 controls	(<70 mm)	8.9% 26/292	9.8% 35/357	29.1% 25/86	25.2% 32/127	36% 9/25	25% 8/32
Ramzy et al[5d]	Retrospective cohort. 39 fibroid patients, 367 controls	32 ± 11 mm	12.5% 16/128	13.8% 165/1192	38.5% 15/39	33.5% 123/367	16.7% 3/18	12.3% 19/154
Eldar-Geva et al[9d]	Retrospective cohort. 46 fibroid patients, 249 controls	24 ± 7 mm	6.6% 9/137	12.3% 94/763	16.4% 9/55	30.8% 98/318	33.3% 3/9	16.3% 16/98
Stovall et al[15]	Retrospective cohort (included both IVF and zygote intrafallopian transfer cycles). 91 fibroid patients, 91 controls	29 mm (10-54 mm)	13.8% 46/334	19.7% 65/330	37.4% 34/91	52.7% 48/91	12.5% *(4/32)*	8.3% *(4/48)*
Hart et al[16]	Prospective observational cohort.112 fibroid patients, 322 controls	23 ± 11 mm (10-50 mm)	12.2% 21/172	20.2% 123/609	23.3% 20/86	34.1% 99/290		
Surrey et al[17d]	Retrospective cohort. 73 fibroid patients, 441 controls.	23 ± 5 mm	20.2% 50/248	23.7% 293/1237	50.7% 37/73	58.4% 191/327		
Jun et al[18]	Retrospective cohort. 141 fibroid patients, 406 controls.	19 ± 13 mm (<70 mm)			30.5% 43/141	41.6% 169/406		
Yarali and Bukulmez[19]	Retrospective cohort. 108 study patients, 324 controls	31 ± 20 mm (10-80 mm)	9.8% 18/183	11.2% 102/911	21.9% 16/73	27.8% 90/324	6.3% 1/16	6.7% 6/90
Check et al[20]	Prospective observational cohort. 61 study patients, 61 controls.	18 ± 11 mm (5-51 mm)			34.4% 21/61	47.5% 29/61		
Wang and Check[21]	Retrospective cohort in ovum donor recipients. 49 study patients, 73 controls.	30 mm (<60 mm)	29.9% 47/157	27.4% 60/219	59.2% 29/49	46.6% 34/73	34.5% 10/29	5.9% 2/34
Oliveira et al[22]	Retrospective age matched cohort. 245 fibroid patients, 245 controls.	19 mm (4-69 mm)			47.8% 117/245	44.9% 110/245	15.9% 39/245	13.1% 32/245
Bulletti et al[23d]	Patients undergoing 1-3 cycles of IVF after myomectomy or expectant management of fibroids	(>50 mm)			No denominator	No denominator given	23.1% 3/13	28.6% 8/28
Benson et al[24]	Prospective, age-matched cohort. 143 fibroid patients, 715 controls.	33 ± 21 mm					14.0% 20/143	7.6% 54/715
Gianaroli et al[25]	Retrospective age-matched cohort. 75 fibroid patients, 127 controls.	18 ± 14 mm	18% 47/261	26.4% 73/276	34.9% 45/129	41.1% 53/129	40% 18/45	18.9% 10/53

Continued on page 360.

TABLE 2
Intramural fibroids: controlled studies

Continued from page 359.

	Study design; number of patients	Fibroid diameter: mean (range)	Implantation rate[a]		Clinical pregnancy rate[b]		Spontaneous abortion rate[c]	
			Fibroids	No fibroids	Fibroids	No fibroids	Fibroids	No fibroids
Khalaf et al[26d]	Prospective observational cohort: follow-up outcomes from Hart et al[16]	Not reported					36.1% 13/36	27.3% 44/161
Feinberg et al[27]	Retrospective cohort. 183 fibroid patients, 1044 controls.	25 mm	25.6% 103/402	31.1% 683/2199	35% 64/183	43.2% 451/1044	25.0% 16/64	16.6% 75/451
Casini et al[14]	Prospective, observational. *Spontaneous* conceptions, following timed intercourse. 42 fibroid patients, 40 "controls" s/p myomectomy.	(>40 mm)			40.5% 15/37	38.5% 15/39		
Klatsky et al[6]	Retrospective cohort oocyte donor recipients. 94 fibroid patients, 275 controls.	28 mm (10-81 mm)	36.9% 75/203	37.0% 227/614	48.8% 44/94	54.2% 149/275	18.2% 8/44	9.4% 14/149
Exacoustos and Rosati[31] (n = 492)	Prospective cohort including pregnancies up to 20 weeks.	Not reported					7.7% 38/492	6.8% 829/12,216
Cumulative rates			18.2% *458/2517* OR 0.79 (0.71-0.88)	22.1% *1920/8707*	36.9% *519/1405* OR 0.84 (0.74-0.95)	41.1% *1676/4077*	15.3% *185/1121* OR: 1.34 (1.04, 1.65) 20.4%[e] *147/719*[e] OR 1.82 (1.43-2.30)	7.7% *1121/14,474* 12.9%[e] *292/2258*[e]

IM, intramuscular; *IVF*, in vitro fertilization; *OR*, odds ratio.

[a] No. of sacs per no. of embryos transferred.

[b] Most studies defined clinical pregnancy as a cycle resulting in either a living embryo or gestational sac. Hart et al included chemical pregnancies.

[c] Clinical miscarriage after documented clinical pregnancy.

[d] Included repeat cycles in the same patient.

[e] Limited to patients with early first-trimester ultrasounds.

Klatsky. Fibroids and reproductive outcomes. Am J Obstet Gynecol 2008.

28.3%, respectively). Unfortunately, the fibroid cohort was significantly older by 2 years, which may have confounded the treatment outcomes attributable to patients with fibroids. This same study group subsequently reported lower pregnancy rates in the same cohort of patients undergoing repeat cycles of IVF.[26] Certainly, they identified a poorer prognosis group, but whether the difference is attributable to fibroids, maternal age, or other factors remains unclear, and these findings have not been consistently reproduced by other age-matched cohort studies.[6,17-20,22,27]

In 2004, Oliveira et al[22] reported lower pregnancy rates in a subgroup of patients with intramural or subserosal fibroids larger than 4 cm when compared with patients with fibroids smaller than 4 cm in maximum diameter. However, these investigators found no significant difference in their primary outcome of live birth rate in patients with and without fibroids. These findings are not consistent with those of Hart et al[16] and Feinberg et al[27] whose study cohorts had mean fibroid diameters of 2.3 cm and 2.6 cm. In Oliveira et al,[22] the cohort with fibroids 1.0-4.0 cm demonstrated a trend toward higher pregnancy rates than the cohort without fibroids (P = NS). No other study has documented a clear adverse relationship between the size of the fibroids and poorer implantation or pregnancy rates. We recently reported that subjects with fibroids ranging from 4-8 cm had a 67% ongoing pregnancy rate with a nonsignificant trend toward

higher pregnancy rates than controls and women with smaller fibroids.[6] At this point, there is no compelling evidence that larger intramural fibroids exert a worse impact on ongoing pregnancy rates. Many studies also excluded patients with fibroids larger than 5 or 7 cm.[7,16,22]

With such disparate findings, meta-analysis can be a useful tool; however, it is prone to replicating and amplifying biases in earlier studies and reinforces publication biases favoring studies with positive findings. Table 2 summarizes the findings of individual studies. Each study has strengths and limitations. Hart et al[16] is a well-conducted prospective observational study, but was not age matched. Several larger, age-matched retrospective studies were also well conducted and reported negative findings; however, each was limited by a lack of power to detect statistically significant outcomes.[17-19] Feinberg et al[27] conducted an excellent study to assess the role of African American ethnicity in IVF outcomes and secondarily found a deleterious effect of fibroids on delivery rates. We were unable to replicate the findings of Hart et al or Feinberg et al in an adequately powered study of ovum donor IVF recipients undergoing embryo transfer.[6]

We provide cumulative data summarizing the findings of these studies in Table 2, but urge caution when interpreting these numbers, as this approach replicates individual study and age biases, as well as a global publication bias favoring positive studies. That said, when relevant study cohorts are reviewed together, intramural fibroids appear to be associated with a slight decrease in implantation rate, from 22% to 18%, and an increase in spontaneous abortion rate, from 8% to 15%. Although we believe it reasonable to offer hysteroscopic myomectomy to patients with submucosal fibroids, more prospective studies are needed to confirm a deleterious effect independent of ovarian age, before we would recommend removal of intramural fibroids for reproductive optimization.

Miscarriage

The most frequently cited study on the relationship between fibroids and fertility outcomes is a review of published reports from 1957-1980, which identified a decrease in miscarriage rates from 41% to 19%, in a cohort of women with *symptomatic* fibroids who underwent myomectomy.[28] Most of the studies included were small case series without controls that were subject to various methodologic limitations. In addition to the recall and ascertainment bias associated with case series, patients in this study were different because they had symptomatic, palpable fibroids. Most infertility patients today are asymptomatic with the fibroid diagnosis made by ultrasonography. A small, uncontrolled series of 19 asymptomatic patients who conceived with fibroids reported a reduction in spontaneous miscarriages post-myomectomy compared with the pre-myomectomy rate (24% vs 60%, respectively).[29]

A larger, controlled study by Benson et al[30] reported a nearly 2-fold increase in miscarriage rate among 143 patients with sonographically identified fibroids that were identified on first-trimester ultrasound, when compared with more than 715 age-matched controls without fibroids (14.0% vs 7.6%, $P < .05$). Although fibroid size was not associated with the spontaneous loss rate, the presence of multiple fibroids was a significant predictor of spontaneous loss and among the 88 patients with only a single fibroid, there was no increased risk of spontaneous miscarriage compared with controls. Feinberg et al[27] did not report on the number or size of fibroids but found a trend toward increased miscarriages in 64 pregnancies with intramural fibroids compared with 451 pregnancies in patients without fibroids (25.0% vs 16.1%, respectively).

Many of the previously mentioned studies documented trends toward a higher spontaneous abortion rate in women with intramural fibroids, but were designed to examine pregnancy rates with IVF and were thus underpowered to individually address the risk of miscarriage. When examined together, these trends begin to look significant. In 8 controlled studies that reported spontaneous abortions in pregnancies resulting from IVF, women with intramural fibroids had a spontaneous abortion rate of 22.0%, compared with 15.4% in controls (Table 2). After including data from the study by Benson et al,[30] women undergoing first-trimester ultrasounds with intramural fibroids appear significantly more likely to experience a spontaneous miscarriage, 20.4% vs 12.9% (odds ratio [OR], 1.6; 95% confidence interval [CI], 1.3-2.0). Of note, the study by Exacoustos et al[31] is unique because of exclusion criteria with a maximum fibroid diameter of less than 3.0 cm and inclusion criteria of screening ultrasounds up to 20 weeks' gestation. This study was excluded from our cumulative data set and found a lower miscarriage rate with fibroids, when compared with studies that included only subjects with early first-trimester ultrasounds.

Data are unavailable to evaluate the risk of miscarriage in women with submucosal fibroids. Casini et al[14] reported miscarriages in 5 of 9 (53%) pregnant women with submucosal fibroids and miscarriages in 9 of 21 (43%) women who underwent prior myomectomy and only 1 patient in the Benson et al[24] study had a submucosal fibroid.

Fibroids in Pregnancy

The effects of fibroids on pregnancy outcomes and complications are even more ambiguous. Most reports use retrospective cohort or case-control study designs, which are subject to ascertainment biases, identifying fibroids after patients have pain develop, undergo cesarean delivery, or develop other complications of pregnancy. The most commonly reported complaint associated with uterine fibroids during pregnancy is pain.[32] Acute pain episodes can be severe enough to warrant hospitalization for analgesia. A review of antepartum admissions for fibroid-related pain exacerbations found ibuprofen to be the most effective analgesic. However, nonsteroidal antiinflammatory drugs (NSAIDs) are usually avoided in the third trimester because of the associated fetal and neo-

TABLE 3
Labor and delivery complications

Study (n = patients with fibroids)	Cesarean	Malpresentation	Labor dystocia	Postpartum hemorrhage	Retained placenta	Chorio or endometritis
Vergani et al[41] (n = 183)	+	N/A	N/A	−	−	N/A
Davis et al[43] (n = 85)	N/A	N/A	N/A	N/A	N/A	N/A
Rice et al[38] (n = 93)	+	+[a]	N/A	+ (PP hysterectomy)	N/A	N/A
Exacoustos and Rosati[31] (n = 492)	−	N/A	N/A	+ (PP hysterectomy)	N/A	+(endometritis)
Qidwai et al[39] (n = 401)	+[b]	+	−	+	N/A	−
Sheiner et al[44] (n = 690)	+	N/A	N/A	N/A	N/A	N/A
Benson et al[30]	+	N/A	N/A	N/A	N/A	N/A
Coronado et al[40] (n = 2065)	+	+	+	−	N/A	N/A
Roberts et al[45] (n = 51)	+	−	N/A	−	N/A	N/A
Vergani et al[42] (n = 251)	+	+	−	+	−	N/A

PP, postpartum.
(+) positive association with $P < .05$.
(−) negative association, $P \geq .05$.
(N/A) not examined/reported.

[a] Reported increased malpresentation associated with the size of the largest fibroid.

[b] Reported no difference in rate of operative vaginal deliveries.

Klatsky. Fibroids and reproductive outcomes. Am J Obstet Gynecol 2008.

natal risks of early closure of the fetal ductus arteriosus, pulmonary hypertension, decreased fetal renal function, oligohydramnios, necrotizing enterocolitis, intracranial hemorrhage, and a concern for maternal platelet dysfunction.[33]

Although initial hypotheses suggested that pain was secondary to fibroid growth during pregnancy, painful episodes appear to be unrelated to absolute fibroid size or growth.[32] Prospective, longitudinal studies have also failed to document significant change in fibroid size during pregnancy.[34-37] Edema and local areas of infarction are other commonly proposed mechanisms for pain. The strong analgesic effect of NSAIDS suggests that symptoms are due to prostaglandins released from cellular damage in fibroids. When pain is severe, it is more often accompanied by sonographic findings of anechoic or cystic spaces in the fibroids; however, this finding is nonspecific and can be seen in asymptomatic lesions as well.[31,32]

Obstetric Outcomes

Several investigators have reported on obstetric outcomes in patients with fibroids. Although the studies are inconsistent and use different methodologies for retrospectively ascertaining the presence of fibroids with subsequent conflicting findings, several preliminary conclusions can be described. Tables 3 and 4 describe studies assessing antepartum and peripartum complications in women with fibroids. Unfortunately, a lack of power to evaluate uncommon outcomes together with a risk of ascertainment bias in positive studies prohibits more definitive conclusions. We report the cumulative data from each of the studies reviewed (Table 5). We caution the reader because these data do not account for confounding variables in women with fibroids and may amplify bias related to advanced maternal age and a higher likelihood to diagnose fibroids in complicated pregnancies.

Mode of delivery

The weight of the evidence supports a causative role for fibroids in higher rates of cesarean delivery, particularly in women with larger fibroids (Table 3). Despite its adequate size and prospective documentation, Exacoustos et al[31] did not find a higher incidence of operative deliveries; however, every other study that assessed mode of delivery found a higher cesarean rate among women with fibroids, 48.8% compared with 13.3% (Table 3). The most common cause of the higher cesarean rates appears to be malpresentation.[38-42] When studies prospectively examine labor curves in women with documented fibroids, no difference was seen in patients with fibroids. Coronado et al[40] reported higher rates of labor dystocia; however, they identified fibroid patients from International Classification of Diseases (ICD) codes charted retrospectively at discharge. These data likely reflect a significant ascertainment bias because many patients may have had fibroids diagnosed at the time of cesarean, which was more likely to occur in patients with abnormal labor curves.[40] Conversely, both Vergani et al[42] and Qidwai et al[39] reported high vaginal delivery rates among labor-eligible women with very large fibroids and concluded that women with large fibroids should not be counseled against a trial of labor.

TABLE 4
Antepartum complications

Study (n = patients with fibroids)	IUGR	Preterm labor or delivery[a]	Placenta previa	First-trimester bleeding	Abruption	PPROM
Vergani et al[41] (n = 183)	−	−	−	N/A	−	−
Davis et al[43] (n = 85)	−	+	N/A	N/A	N/A	+
Rice et al[38] (n = 93)	−	+	N/A	N/A	+	N/A
Exacoustos and Rosati[31] (n = 492)	−	−PTD +PTL	N/A	+	+	−
Qidwai et al[39] (n = 401)	N/A	+	+	N/A	−	−
Sheiner et al[44] (n = 690)	N/A	+	N/A	N/A	+	N/A
Coronado et al[40] (n = 2065)	+[b]	+[c]	−	+	+	N/A (+PROM)
Roberts et al[45] (n = 51)	−	−	N/A	−	N/A	−
Vergani et al[42] (n = 251)	−	−	+	N/A	−	−

IUGR, intrauterine growth rate; *PPROM*, preterm premature rupture of membranes; *PROM*, premature rupture of membranes.
(+) positive association with $P < .05$.
(−) negative association, $P \geq .05$.
(N/A) not examined/reported.

[a] Preterm labor required hospitalization and tocolysis.

[b] Reported more infants <2500 g but did not control for preterm deliveries/gestational age.

[c] Reported increased deliveries before 38 weeks.

Klatsky. Fibroids and reproductive outcomes. Am J Obstet Gynecol 2008.

TABLE 5
Cumulative obstetric outcomes from included studies

	Fibroids	No fibroids	*P* value	Unadjusted OR (95% CI)
Cesarean	48.8% (2098/4322)	13.3% (22,989/173,052)	<.001	3.7 (3.5-3.9)
Malpresentation	13.0% (466/3585)	4.5% (5864/130,932)	<.001	2.9 (2.6-3.2)
Labor dystocia	7.5% (260/3471)	3.1% (4703/148,778)	<.001	2.4 (2.1-2.7)
Postpartum hemorrhage	2.5% (87/3535)	1.4% (2130/153,631)	<.001	1.8 (1.4-2.2)
Peripartum hysterectomy	3.3% (18/554)	0.2% (27/18,000)	<.001	13.4 (9.3-19.3)
Retained placenta	1.4% (15/1069)	0.6% (839/134,685)	.001	2.3 (1.3-3.7)
Chorio or endometritis	8.7% (78/893)	8.2% (2149/26,090)	.63	1.06 (0.8-1.3)
IUGR	11.2% (112/961)	8.6% (3575/41,630)	<.001	1.4 (1.1-1.7)
Preterm labor	16.1% (116/721)	8.7% (1577/18,187)	<.001	1.9 (1.5-2.3)
Preterm delivery	16.0% (183/1145)	10.8% (3433/31,770)	<.001	1.5 (1.3-1.7)
Placenta previa	1.4% (50/3608)	0.6% (924/154,334)	<.001	2.3 (1.7-3.1)
First-trimester bleeding	4.7% (120/2550)	7.6% (1193/15,732)	<.001	0.6 (0.5-0.7)
Abruption	3.0% (115/4159)	0.9% (517/60,474)	<.001	3.2 (2.6-4.0)
PPROM	9.9% (123/1247)	13.0% (7319/56,418)	.003	0.8 (0.6-0.9)
PPROM or PROM	6.2% (217/3512)	12.2% (7425/60,661)	<.001	0.5 (0.4-0.6)

CI, confidence interval; *IUGR*, intrauterine growth rate; *OR*, odds ratio; *PPROM*, preterm premature rupture of membranes; *PROM*, premature rupture of membranes.

Klatsky. Fibroids and reproductive outcomes. Am J Obstet Gynecol 2008.

Placenta previa is a less common outcome and was positively associated with fibroids in 2 studies.[39,42] Two other studies found no association with placenta previa, making this association difficult to ascribe to fibroids as advanced maternal age and prior uterine surgery were not considered[40,41] (Table 4).

Fetal/neonatal morbidity

The most common cause of neonatal morbidity reported in any of these studies was preterm delivery. Five studies have reported earlier gestational ages at delivery in women with fibroids with an additional study reporting a higher incidence of hospitalization for threatened preterm labor in patients with fibroids (Table 4).[31,38-40,43,44] Delivery and hospitalization may have been secondary to increased incidence of pain syndromes in women with fibroids, resulting in a decision to proceed with an early delivery.

Conversely, the weight of the evidence suggests that these patients are not at higher risk for preterm premature rupture of the membranes (PPROM).[31,39,41-43,45] Only 1 small study suggested an increase in PPROM rates[43] and a second study reported an increase in PPROM at term. However, this latter study was subject to the earlier described ascertainment bias and may have selected for patients with abnormal labor curves.[40] In fact, the cumulative data suggest a mild ameliorative effect of fibroids on rates of PPROM.

Despite concerns about placentation, no single study has been able to demonstrate a higher rate of intrauterine fetal growth restriction among women with fibroids. Birthweights were similar in 6 studies (Table 4).[31,38,41-43,45] Only 1 study reported a higher incidence of birthweights under 2500 g in pregnancies with fibroids; however, the analyses did not adjust for gestational age at delivery, which was lower in patients with fibroids.[40] Our cumulative data suggest that these women may be at slightly increased risk of delivering small-for-gestational-age infants; however, these data do not control for maternal or gestational age and there is no evidence that myomectomy would ameliorate this risk.

Placental abruption is a rare but potentially devastating outcome that has been inconsistently associated with fibroids (3 negative and 4 positive studies). In studies that found a positive association, the strongest correlation was documented in patients with submucosal or retroplacental fibroids.[31,38,44,40] Providers should be aware that these patients may be at higher risk for abruption; however, myomectomy has not been shown to decrease this risk and the background risk remains low.

Postpartum complications

The most common postpartum complication with fibroids is postpartum hemorrhage (PPH), likely caused by decreased uterine contractility in women with fibroids. Although the data are conflicting, 4 studies demonstrated a positive association with bleeding or severe atony,[31,38,39,42] whereas 2 studies did not find a difference (Table 3).[40,45] The increased requirement for emergency hysterectomy in women with fibroids reported in 2 studies supports the hypothesis that the altered contractility of a uterus with fibroids renders it more prone to hemorrhage.[31,38] In addition, an increased rate in endomyometritis reported by Qidwai et al[39] ceased to be significant after controlling for PPH. Exacoustos et al[31] also reported an increase in postpartum infection rates, but did not control for PPH. Retained placenta is another rare complication that has been examined and does not appear related to fibroid status (Table 4).

Myomectomy

Despite the lack of consensus on the benefits of intramural fibroid resection, there is a wealth of evidence demonstrating that myometrial tissue heals well after myomectomy and that infertility treatments after myomectomy are not compromised by the surgery.[13] Nevertheless, myomectomy should not be performed without a clear indication and evidence of benefit.

As with any surgical procedure, myomectomy carries morbidity and risk for complication. Abdominal and transmural myomectomies often necessitate future cesarean sections and may generate pelvic adhesions that might contribute to subsequent infertility. The economic costs associated with myomectomy as well as the delayed time to infertility treatment initiation must be considered when identifying patients for whom myomectomy could be beneficial.

In complicated pregnancies, myomectomy can be successfully performed in patients with intractable pain from rapidly growing or degenerating subserosal or pedunculated fibroids. In a series of 13 such patients with myomectomy performed before 26 weeks, all delivered at least 7 weeks out from surgery with good neonatal outcomes.[31]

Uterine Artery Embolization

Myomectomy remains the standard of care for treating symptomatic fibroids in women desiring fertility preservation; however, many women are now choosing to undergo uterine artery embolization (UAE) as an alternative to hysterectomy for symptomatic fibroids. The Committee on Gynecologic Practice of American College of Obstetrics and Gynecology considers the desire for future fertility to be a relative contraindication to UAE and many authorities recommend use of contraception for women after the procedure.[46] Nevertheless, successful pregnancies have been reported. Two retrospective studies recently documented 80 pregnancies in 1755 women who underwent UAE.[47,48] An additional report compared outcomes in 53 pregnancies after UAE with women undergoing laparoscopic myomectomy.[49] Although fertility rates cannot be inferred from these data, the outcomes of pregnancies suggest a modest trend toward increasing risk of preterm delivery, postpartum hemorrhage, and abnormal placentation. None of these studies included age-matched controls or cohorts with untreated fibroids. The majority of pregnancies in both studies were carried to term without complication. Sixty-eight percent of the patients underwent cesarean deliveries; however, the majority of these cesareans were elective without a trial of labor.

SUMMARY

Despite the relatively small number of patients studied, the evidence for hysteroscopic myomectomy of submucosal fibroids in patients undergoing assisted reproductive technologies is compelling. That said, controlled trials would help to better assess the benefit of routine preconception hysteroscopic resection of submucosal fibroids.

The effect of intramural fibroids on fecundity is less clear. Intramural fibroids may have a small detrimental affect on ongoing pregnancy rates, likely attributable to a modest decrease in implantation rate and an increase in the risk of spontaneous abortion in implanted pregnancies. However, the modest, if any, clinical impact of these fibroids must be weighed against the cost, morbidity, and treatment delay of myomectomy before pursuing IVF if the lesions are not symptomatic or cavity distorting. The cumulative effects reported herein should be interpreted cautiously, because of the inherent publication bias that is believed to favor positive results, which can have a 3- to 6-fold higher probability of being published.[46,47] Furthermore, the cumulative analysis does not control for confounding factors such as age and number of embryos transferred. Larger, prospective studies are needed to better quantify any risk posed by intramural fibroids based on size, location and number.

In counseling patients with fibroids preconceptually, it is important to recognize that most patients with asymptomatic fibroids can conceive spontaneously. In patients presenting with infertility, submucosal fibroids have been associated with markedly lower ongoing pregnancy rates in small studies, but no randomized, controlled trials evaluating the benefit of hysteroscopic myomectomy have been reported. Women with intramural fibroids should be counseled that there is conflicting evidence on the effect that these fibroids have on infertility, with the cumulative effect of such lesions unlikely to be large. Subserosal fibroids appear to have no effect on fecundity.

The most commonly experienced adverse obstetric outcome in women with fibroids is an increase in cesarean delivery, which is mostly attributable to malpresentation. The risk of preterm labor and delivery also appears to be slightly elevated in these patients. Very large fibroids located near the placenta may place obstetric patients at slightly increased risk during labor, particularly for hysterectomy and postpartum hemorrhage. The association with placental abruption is weak and inconsistent with great variation from study to study. Neonatal outcomes do not appear different from pregnancies in women with fibroids compared with controls.

In addition, patients should be counseled that obstetric risks are usually outweighed by the morbidity, cost, and risk of a major abdominal surgery to remove them before pregnancy. When women with large fibroids present in cephalic presentation and in labor, their likelihood of having a successful vaginal delivery remains high. Most other outcomes influenced by fibroids are rare enough that the absolute risk of having a complication attributable to fibroids is outweighed by the morbidity and risks associated with preconceptual prophylactic myomectomy. In addition, myomectomy is unlikely to reduce the increased risk of cesarean delivery, because the possibility of extensive myometrial dissection or transmural incisions could compel obstetricians to perform elective cesarean deliveries.

Surgery remains best suited for patients with symptomatic fibroids who are good operative candidates and desire preservation of their fertility. Although myomectomy is effective at relieving related pelvic pressure and menorrhagia, its role in fertility enhancement has yet to be well demonstrated.[50,51] ■

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