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Original Article

Effects of myomas and myomectomy on assisted reproductive technology outcomes

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ABSTRACT

Objective: To determine the effects of fibroids, and their removal, on ART outcomes.

Materials and methods: Single institution retrospective cohort study of infertility patients who underwent myomectomy prior to either in vitro fertilization (IVF) or intrauterine insemination (IUI) between August 2006 and October 2015 (N = 49). Two separate control groups were established: 1) women with fibroids left in situ during the ART process (N = 76), and 2) women with no fibroids (N = 103). The study was powered to detect a difference between a 42%, 11%, and 25% live birth (LB) rate in the myomectomy, fibroids in situ, and no fibroids groups at $P < 0.05$.

Results: There were no significant differences in IVF cycle parameters between groups. Fibroids that were either submucosal or intramural with associated cavity distortion were significantly more likely to be removed. Amongst women undergoing IVF, the cumulative incidence of clinical pregnancy (CP) was significantly higher in the myomectomy group than the in situ or no fibroids groups. Women who underwent pre-IVF myomectomy also achieved CP more quickly. Cumulative LB rates did not differ significantly amongst women undergoing IVF. CP and LB rates per cycle were similar between myomectomy, in situ, and no fibroids groups (CP 49% vs. 37.5% vs. 54.4%, $P = 0.21$; LB 41.7% vs. 27.1% vs. 43.9%, $P = 0.17$).

Discussion: IVF outcomes appear to be improved by judicious removal of clinically significant fibroids. Further prospective studies are required to confirm the role of fibroids, and their removal, on ART outcomes before advocating for routine myomectomy amongst women with fibroids undergoing ART.

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Introduction

Fibroids represent the leading cause of hysterectomy in the United States [1] with a cumulative incidence of 70% in women of reproductive age [2]. In addition to the clinical sequelae of menorrhagia and pelvic pressure or pain, it is clear that fibroids can adversely affect reproductive outcomes. These adverse effects include both impaired fertility and adverse obstetric outcomes. Many studies have confirmed the negative impact of fibroids on obstetric outcomes including increased risk of preterm labor and delivery, placenta previa, intrauterine growth retardation, increased rate of cesarean section, and postpartum hemorrhage [3–5]. Their impact on fertility, however, remains less clear.

The impact of fibroids on fertility outcomes has long been debated. A number of studies have examined the effects of fibroids in women undergoing assisted reproductive technology (ART) and

have produced conflicting results, with data to both support and dismiss the negative impact of fibroids on pregnancy rates [6–12]. These contradictory results can at least partially be attributed to heterogeneity in patient inclusion criteria and primary endpoints as well as methodological flaws such as failure to control for confounding factors and lack of adequate power. Perhaps the most significant shortcoming is the inappropriate choice of control group. In order to draw valid conclusions, both the treatment and control groups should be afflicted by the condition in question. Rather than comparing women who undergo myomectomy with infertile controls without fibroids, the treatment group should be compared with women who have fibroids left in situ. Performed in the 1990s, the only two adequately controlled studies to date are now largely outdated given the significant advances in both ART and surgical techniques over the past three decades [13,14].

The inconclusive evidence regarding the association between fibroids and fertility has made it difficult for clinicians to interpret the existing data and emphasizes the need for high-quality, appropriately controlled studies. Thus, the primary aim of this study is to determine the effects of fibroids, and their removal, on

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clinical pregnancy (CP), implantation, miscarriage, and live birth (LB) rates, as well as time to pregnancy, in women undergoing in vitro fertilization (IVF) and intrauterine insemination (IUI).

Materials and methods

This retrospective chart review was approved by the institutional review board. Patients eligible for study inclusion were identified by searching CPT and ICD codes. Women met inclusion criteria if they were ≤ 45 years old and undergoing ART (either IUI or IVF) between August 2006 and October 2015 at our institution for primary or secondary infertility with at least 18 months of follow-up with attempts to conceive. Patients who previously underwent myomectomy were excluded. The intervention group comprised women who underwent myomectomy prior to undergoing ART (“myomectomy” group). Two separate control groups were established: 1) women with fibroids left in situ during the ART process (“in situ” group), and 2) women with no fibroids (“no fibroids” group). Once all the women in the “myomectomy” and “in situ” groups were identified, women in the “no fibroids” group were selected randomly from a pool of all women undergoing ART at our institution during the defined study period. The study was powered to detect a difference between a 42%, 11%, and 25% LB rate in the myomectomy, fibroids in situ, and no fibroids groups, respectively, at $P < 0.05$.

The electronic medical record of each patient was searched to obtain demographic and clinical information, as well as subsequent fertility outcomes. For patients with fibroids, detailed information was obtained from imaging reports. In patients undergoing myomectomy, operative notes were reviewed to determine surgical approach. We also collected information specific to the ART process. For those who underwent more than ten cycles, detailed information was only collected from the first ten cycles. The following definitions were used: CP rate = cases of sonographic fetal cardiac activity/total # ART cycles, implantation rate = # gestational sacs with fetal cardiac activity/total # embryos transferred, LB rate = cases of delivery of \geq one infant/total # ART cycles. CP rate per LB rate was used to represent the spontaneous abortion rate. Finally, time to first pregnancy was calculated as the number of months from the first ART cycle to first CP.

Categorical factors were summarized using frequencies and percentages, while continuous measures summaries used medians and interquartile ranges. To evaluate categorical factors, Pearson chi-square and Fisher Exact tests were used, and ANOVA and Kruskal-Wallis tests were used for continuous factors. All tests were two-tailed and performed at a significance level of 0.05. Analysis was performed using SAS software (version 9.4; Cary, NC).

Results

A total of 228 patients met inclusion criteria: 49 in the myomectomy group, 103 in the no fibroids group, and 76 in the in situ group. As some women underwent both IVF and IUI cycles, outcomes were analyzed by cycle rather than by individual patient. Women in the no fibroids group underwent a total of 282 ART cycles (including both IVF and IUI), women in the in situ group underwent 206 ART cycles, and women in the myomectomy group underwent 112 ART cycles.

Table 1 summarizes the demographic and baseline characteristics by group. Patients with no fibroids were significantly younger than the in situ and myomectomy groups (36.3 vs. 37.2 vs. 37.6 years, $P=0.026$). Individuals in the no fibroids group were also significantly more likely to be Caucasian in comparison to the in situ and myomectomy groups ($P < 0.001$). For patients in the myomectomy group, infertility was more often due to tubal factor ($P=0.003$) whereas the in situ group infertility was more often due

Table 1
Demographics/baseline clinical information by group.

Factor	No Fibroids (N = 103)	Fibroids in Situ (N = 76)	Myomectomy (N = 49)	P
Age at first ART	36.3 \pm 0.91	37.2 \pm 4.2	37.6 \pm 3.3	0.026^a
Race ^e				<0.001^c
Caucasian	100 (97.1)	58 (76.3)	22 (46.8)	
African American	3 (2.9)	13 (17.1)	18 (38.3)	
Other	0 (0.0)	5 (6.6)	7 (14.9)	
BMI	28.5 \pm 7.2	28.4 \pm 7.2	30.5 \pm 7.4	0.21 ^a
Infertility Diagnosis:	24 (23.3)	12 (15.8)	16 (32.7)	0.089 ^f
Male factor				
Infertility Diagnosis:	6 (5.8)	8 (10.5)	12 (24.5)	0.003^f
Tubal factor				
Infertility Diagnosis:	24 (23.3)	10 (13.2)	4 (8.2)	0.039^f
Anovulation				
Infertility Diagnosis:	5 (4.9)	14 (18.4)	4 (8.2)	0.010^f
Endometriosis				
Infertility Diagnosis:	39 (37.9)	28 (36.8)	8 (16.3)	0.020^f
Unexplained				
Infertility Diagnosis:	3 (2.9)	6 (7.9)	2 (4.1)	0.28 ^d
Other				
AMH (ng/ml) ^g	1.7 [0.60,3.3]	0.90 [0.43,2.0]	1.00 [0.31,2.2]	0.024^b

^a Data not available for all subjects. Missing values: Race = 2, AMH (ng/ml) = 79. Values presented as Mean \pm SD, Median [P25, P75], or N (column %). p-values: a = ANOVA, b = Kruskal-Wallis test, c = Pearson's chi-square test, d = Fisher's Exact test.

to endometriosis ($P=0.010$) and the no fibroids group infertility was more often due to anovulation ($P=0.039$) and unexplained infertility ($P=0.020$). The no fibroids group was found to have a higher median AMH compared to the myomectomy group and the in situ group (1.7 vs. 1.0 vs. 0.9, $P=0.024$). BMI was evenly distributed between the three groups. For individuals who underwent IVF, there were no differences between the three groups when comparing medication protocols, number of stimulation days, number of eggs retrieved, number of mature oocytes, number of embryos fertilized and numbers of embryos transferred.

Specific details about the fibroids are compared between the in situ and myomectomy groups in Table 2. Submucosal fibroids and intramural fibroids with cavity distortion were significantly more likely to be removed ($P < 0.001$, $P=0.001$). Compared to the in situ group, individuals in the myomectomy group had a greater average number of fibroids (3 vs. 2, $P < 0.001$), and larger diameter of the dominant fibroid (56 mm vs. 28.5 mm, $P=0.002$). Fibroids were diagnosed via transvaginal ultrasound (TVUS) in 75.2% of women, magnetic resonance imaging (MRI) in 17.6% of women, saline infusion sonohysterography (SIS) in 26.4% of women, hysteroscopy in 36.8% of women, and via hysterosalpingogram (HSG) in 37.6% of

Table 2
Fibroid information by group.

Factor	Total (N = 125)	Fibroids in Situ (N = 76)	Myomectomy (N = 49)	P
Fibroid Locations:	86 (68.8)	56 (73.7)	30 (61.2)	0.14 ^c
Intramural				
Fibroid Locations:	31 (24.8)	5 (6.6)	26 (53.1)	<0.001^c
Submucosal				
Fibroid Locations:	58 (46.4)	31 (40.8)	27 (55.1)	0.12 ^c
Subserosal				
Total # of Fibroids	2.0 [1.00,3.0]	2.0 [1.00,2.0]	3.0 [1.00,5.0]	<0.001^b
Diameter of largest fibroid (mm)	33.5 [20.5,58.0]	28.5 [18.5,42.0]	56.0 [21.5,75.5]	0.002^b
Intramural w/ cavity distortion? ^g	26 (31.0)	10 (17.9)	16 (57.1)	0.001^c

^a Data not available for all subjects. Missing values: Diameter of largest fibroid (mm) = 1, Intramural w/ cavity distortion? = 41. Values presented as Mean \pm SD, Median [P25, P75], or N (column %). p-values: b = Kruskal-Wallis test, c = Pearson's chi-square test.

women. Most women were imaged with more than one modality. Of the 49 women who underwent myomectomy, 17 (34.7%) had fibroids removed hysteroscopically, 20 (40.8%) had fibroids removed using a minimally invasive approach (laparoscopic or robotic) and 23 (46.9%) had fibroids removed via laparotomy or mini-laparotomy. Of note, some patients underwent more than one surgical approach during the same surgery.

Fig. 1 compares the cumulative incidence of CP between the three groups amongst those who underwent IVF. In the myomectomy group, women achieved CP more quickly and had a higher cumulative incidence of CP when compared to the in situ and no fibroids group ($P=0.007$). At three months following initial treatment, CP rate was 0.37 (95%CI 0.25–0.52) in the myomectomy group, compared to 0.14 (95%CI 0.08–0.25) in the in situ group and 0.16 (95%CI 0.10–0.24) in the no fibroids group. At six months following initial treatment, the CP rate was 0.43 (95%CI 0.30–0.58) in the myomectomy group, compared to 0.17 (95%CI 0.10–0.28) in the in situ group and 0.17 (95%CI 0.11–0.26) in the no fibroids group. At nine months following initial treatment, the CP rate was 0.47 (95%CI 0.34–0.62) in the myomectomy group, compared to 0.20 (95%CI 0.12–0.31) in the in situ group and 0.19 (95%CI 0.13–0.28) in the no fibroids group. There was no difference found between the in situ and no fibroid groups.

Supplemental Fig. 1 similarly compares the cumulative incidence of CP between the three groups amongst those who underwent IUI. This comparison revealed that the no fibroid group had a greater CP rate and total cumulative incidence in comparison to the in situ and myomectomy groups. At three months following initial treatment, the CP rate was 0.18 (95%CI 0.12–0.27) in the no fibroid group, compared to 0.08 (95%CI 0.04–0.17) in the in situ group and 0.04 (95%CI 0.01–0.15) in the myomectomy group. At six months following initial treatment, the CP rate was 0.24 (95%CI 0.17–0.34) in the no fibroid group, compared to 0.11 (95%CI 0.05–0.20) in the in situ group and 0.04 (95%CI 0.01–0.15) in the myomectomy group. At nine months following initial treatment, the CP rate was 0.27 (95%CI 0.20–0.37) in the no fibroid group, compared to 0.12 (95%CI 0.06–0.22) in the in situ group and 0.04 (95%CI 0.01–0.15) in the myomectomy group.

Supplemental Fig. 2 describes the CP rate in relation to number of IVF cycles completed. There were no significant differences between the groups in either two or three-way comparisons.

Supplemental Fig. 3 describes the CP rate in relation to the number of IUI cycles completed. There were no significant differences between the myomectomy and in situ groups or the in situ and no fibroids groups in two-way comparisons. There was a significant difference between the myomectomy and no fibroids group ($P=0.02$) and between all three groups in a three-way comparison ($P=0.02$).

Fig. 2 describes the LB rate in relation to the number of IVF cycles completed. There were no significant differences between the groups in either two or three-way comparisons. Supplemental Fig. 4 describes the LB rate in relation to the number of IUI cycles completed. There were no significant differences between the myomectomy and in situ groups or the in situ and no fibroids groups in two-way comparisons. There was a significant difference between the myomectomy and no fibroids group ($P=0.02$) and between all three groups in a three-way comparison ($P=0.02$).

In addition to analyzing cumulative incidences, we also looked at our outcomes per cycle (Supplemental Tables 1 and 2). For those who underwent IVF, implantation rates were significantly higher in the no fibroids group in comparison to the in situ and myomectomy groups ($P=0.02$). Otherwise, there were no observed differences in outcomes. For those who underwent IUI, there were no significant differences between groups in any of the outcomes. Multivariate models were constructed to adjust for the factors that demonstrated significance in the univariate analyses (age, race, AMH level, and infertility diagnoses). There were no significant differences in any of these per cycle outcomes after adjusting for these factors.

Finally, we compared outcomes between women in the myomectomy and in situ groups including only those with intramural fibroids causing cavity distortion (Supplemental Tables 3 and 4). For IVF treatment cycles, there were no significant differences in CP, LB, miscarriage or implantation rates. For IUI treatment cycles, there were no myomectomy cases of intramural fibroids with cavity distortion for comparison to the in situ group.

Discussion

Our findings indicate that the cumulative incidence of CP improves significantly after myomectomy in women undergoing IVF. The improvement is seen almost immediately, with the

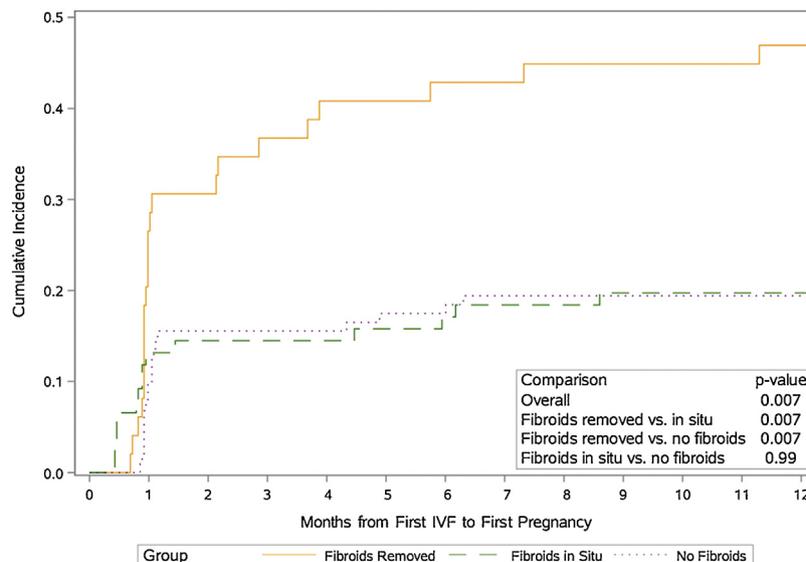


Fig. 1. Cumulative incidence of clinical pregnancy with IVF. Cumulative incidence of clinical pregnancy in relation to number of months until first clinical pregnancy amongst women undergoing IVF.

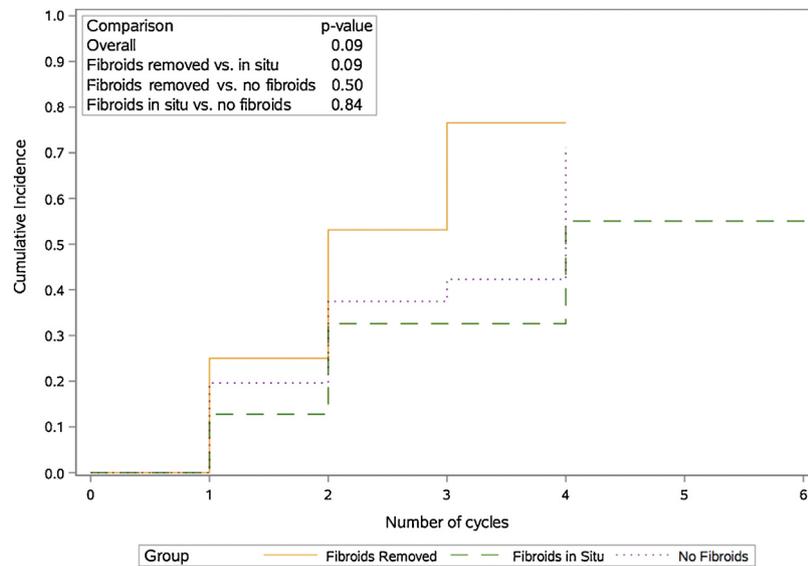


Fig. 2. Cumulative incidence of live birth with IVF.

Cumulative incidence of live birth in relation to number of cycles completed amongst women undergoing IVF.

steepest incline occurring just one month after the first IVF cycle. This is supported by prior research that demonstrated shorter interval to pregnancy in infertile women who underwent hysteroscopic removal of fibroids larger than 2 cm in diameter as compared to infertile women with normal cavities [15]. One plausible interpretation of our findings is that in the setting of IVF, the selection of infertility patients with fibroids for surgery is being done appropriately and fibroid removal restored normal fertility in many of these women. Of particular interest is our finding that women who underwent pre-IVF myomectomy achieved CP more quickly. While LB rates were highest amongst pre-IVF myomectomy patients, this difference did not quite reach statistical significance ($P=0.09$). Thus, while CP is more likely and occurs more quickly in women who undergo myomectomy prior to IVF, these data do not necessarily translate into a higher LB rate. These findings are extremely clinically relevant and may be valuable when counseling the infertile patient with fibroids.

When we looked at our outcomes per cycle rather than as cumulative rates, CP, implantation, and LB rates all did not differ significantly between the three groups. This is in contrast to the results reported by a recent stratified analysis which found that women who underwent hysteroscopic myomectomy for submucosal fibroids had significantly higher CP rates than women with fibroids left in situ, although comparable CP rates to women without fibroids [16]. While these cross-sectional statistics are easily calculated and therefore commonly measured in ART outcomes research, they fail to account for variability in patient follow up and the potential need for repeated cycles. Longitudinal analyses such as cumulative CP and LB incidences provide a more realistic estimate of the likelihood of ultimate success.

Studying the effects of fibroids on IVF outcomes affords unique advantages because the controlled nature of the procedure eliminates several potential confounding factors such as tubal patency and sperm quantity and quality. These factors are not inherently controlled for with IUI, which potentially explains the lack of improvement in cumulative CP incidence following myomectomy amongst women undergoing IUI. This is in line with findings from a recent prospective randomized multicenter trial, which found similar conception and LB rates in women with fibroids undergoing IUI, although their study was limited to only women with non-cavity distorting fibroids [17].

Fibroids that were either submucosal or intramural with cavity distortion were significantly more likely to be removed. This finding was not surprising as it is well-established that these types of fibroids are associated with poorer ART outcomes including decreased CP and LB rates and increased miscarriage rates [16]. In one study, submucosal fibroids were associated with a 70% reduction in delivery rate [18]. There is also strong evidence to suggest that myomectomy can improve ART outcomes for women with submucosal fibroids [16,19]. Thus, it has become routine practice for most clinicians to remove these fibroids prior to IVF initiation.

Some limitations of our research should be noted. This was a retrospective study, which by nature is prone to selection bias and confounders. We sought to minimize the impact of potential confounders in our study by adjusting for significant variables in our multivariate analysis. The retrospective nature of our study also limited the ability to control the imaging modality used for localization and characterization of fibroids. The sensitivity of TVUS for detection of intrauterine lesions is as low as 69%, with a specificity of only 11% for identifying submucosal fibroids [20,21]. The sensitivity and specificity of HSG has been estimated to be as low as 50% and 20%, respectively [22–26]. Hysteroscopy, on the other hand, is considered the gold standard for the evaluation of the uterine cavity. Another highly accurate modality, SIS, has a reported sensitivity of 98–100% and specificity of 100% [21,27]. Also highly accurate, MRI, has 100% sensitivity for detection of submucosal fibroids and has significantly less observer variation than other imaging methods [20,28]. The two most commonly used modalities in our study were HSG and TVUS. This limitation potentially impacted the diagnosis and localization of fibroids and likely led to an underestimation of intracavitary involvement.

The primary strength of our study was the appropriate use of women with fibroids in situ as a control group. Of the many prior studies investigating the effect of myomectomy on ART outcomes, only two have been adequately controlled. Bulletti et al. demonstrated a significantly improved LB rate amongst women who underwent pre-IVF myomectomy (25%) when compared to women with fibroids left in situ (12%) [13]. Seoud et al., on the other hand, failed to detect a significant difference in CP rates between women who underwent myomectomy and women with fibroids left in situ (16.9% and 20.8%, respectively, NS) [14]. Of

note, these LB and CP rates are significantly lower than those reported in our study, highlighting the strides that have been made within our field over the last twenty years as well as the importance of up to date research that reflects these advances. The CP and LB rates reported in our study are in line with those reported in other recent studies [29–31].

Our findings are also consistent with prior research in that women with no fibroids in our study were significantly more likely to be Caucasian, younger in age, and have significantly higher AMH levels. It is well-known that the incidence of fibroids increases with age and is highest amongst African American women [17,32–34]. The higher AMH levels amongst women without fibroids in our study could be partially explained by the lower age amongst women in this group, but interestingly has also been demonstrated in two prior studies [17,35]. It is unclear whether decreased ovarian reserve is directly related to the presence of fibroids and warrants further research. Although AMH levels differed significantly between groups, this biomarker predicts ovarian response to IVF, not chance of pregnancy [36].

In conclusion, our retrospective analysis demonstrates that IVF outcomes appear to be improved by judicious removal of clinically significant fibroids. Further prospective studies are required to confirm the role of fibroids, and their removal, on ART outcomes before advocating for routine myomectomy amongst women with fibroids undergoing ART.

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Declarations of interest

None.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.jogoh.2019.05.001>.

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