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Original Research Article

A Study Comparing Different Routes of Myomectomy with Fertility Outcome

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Abstract:

Objective: To study the association between the myomectomy route and fertility outcome.

Methods: It was a prospective cohort study. Comparative Treatment Options for Uterine Fibroids and relation with fertility. Reproductive-aged women undergoing surgery for symptomatic uterine fibroids. Used life-table methods to estimate cumulative probabilities and 95% confidence intervals (CI) of pregnancy and live birth by myomectomy route during 12, 24, and 36 months of follow-up. Also conducted 12-month interval-based analyses that used logistic regression to estimate odds ratios (ORs) and 95% confidence intervals for associations of interest. In all analyses, we used propensity score weighting to adjust for differences across surgical routes.

Results: Among 309 women who underwent myomectomy (abdominal=103 hysteroscopic=103, and laparoscopic=103), 68 reported pregnancy and 39 reported live birth during 36 months of follow-up. There was little difference in the 12-month probability of pregnancy or live birth by route of myomectomy overall, or among women intending pregnancy. In interval-based analyses, adjusted ORs for pregnancy were 1.25 (95% CI: 0.71–2.18) for hysteroscopic myomectomy and 1.13 (95% CI: 0.72–1.63) for laparoscopic myomectomy compared with abdominal myomectomy. Among women intending pregnancy, adjusted ORs were 1.2 (95% CI: 0.67–2.31) for hysteroscopic myomectomy and 1.29 (95% CI: 0.72–2.05) for laparoscopic myomectomy compared with abdominal myomectomy. Associations were slightly stronger but less precise for live birth.

Conclusion: There is no significant difference in the chances of conception or delivering a live baby by the various myomectomy routes.

Keywords: Fibroids; Myomectomy; Fertility; Pregnancy, Live-Birth-Rate.

Introduction

Uterine fibroids (UF)are the leading indication for hysterectomy. While the lifetime cumulative incidence of clinical diagnosis is approximately 30%, data from standardized screening of women aged 25–45 years estimated a cumulative incidence of ultrasound-detectable fibroids by age 50 of >70% Depending on their location within the uterus, UF may be associated with impaired fertility. However, research investigating the extent to which fertility outcomes differ based on route of myomectomy is limited.

Myomectomy, the most common uterine-preserving procedure performed for UF in the , accounts for about 22% of all UF surgeries. Considering both inpatient and outpatient procedures in the U.S., the most common surgical route for myomectomy is abdominal (via laparotomy) (>75%), followed by laparoscopic (with our without robotic assistance) (~15%) and hysteroscopic (~10%) routes. According to data from the world, the percentage of abdominal myomectomies increased by 11 percentage points from 2012 through 2016 (while laparoscopic myomectomy decreased), likely due to concerns about morcellation and cancer. Compared with laparoscopic myomectomy, abdominal myomectomy has been associated with longer hospitalizations, higher readmission rates, and greater morbidity.

Abdominal myomectomy tends to be more commonly recommended for patients who have larger uterine volume, multiple UF, and UF that cannot be removed easily by other means. In contrast, laparoscopic myomectomy tends to be recommended for women with smaller uterine volume and subserosal/intramural UF. Hysteroscopic myomectomy is recommended for patients with symptomatic submucous UF.

Prospective cohort studies that compare fertility success across surgical approaches for myomectomy can fill important gaps in the literature. In this report, we examine prospectively the association between route of myomectomy (abdominal, hysteroscopic, and laparoscopic) for UF and the probability of conception and live birth during 36 months of follow-up, censoring women with varying lengths of follow-up and adjusting for potential confounding variables. We hypothesize that surgical route of myomectomy would not be strongly associated with fertility outcomes after accounting for differences in patient and UF characteristics across treatment groups. Evidence-based research is critical to generate the information necessary for patients to choose the surgical route for myomectomy that meets their individual needs, goals, and preferences.

Materials and Methods

The Comparing Treatments Options for Uterine Fibroids. Study is of women who were scheduled for treatment for symptomatic fibroids. The primary objective of the registry was to compare prospectively the effectiveness of different surgical and interventional treatment options (hysterectomy, myomectomy, uterine artery embolization) on patient-reported outcomes postoperatively and during 3 years of follow-up using validated general and disease-specific surveys of quality of life. Details on the study design, protocol, and rationale for COMPARE have been published elsewhere. The registry protocol was reviewed and approved by institute ethical committee.

Trained site coordinators screened all women for eligibility. Eligible participants then provided informed consent. The baseline questionnaire elicited self-reported data on patient socio-demographics, medical history, fibroid history, prior fibroid procedures, current and prior fibroid therapies, reproductive history, measures of financial distress, and child bearing plans. Per protocol, the baseline questionnaire was completed within the 60-day window before the procedure.

Follow-up questionnaires were completed 12, 24, and 36 months after the procedure. Participants completed questionnaires through the web-based portal, at in-person visits, or via telephone interview with the center. If a participant was lost to follow up, coordinators and the local recruitment sites attempted to contact the participant using medical records to ascertain any new contact information.

Assessment of uterine characteristics and myomectomy

Myomectomy was performed according to professional standards and institutional protocols at each clinical site. The choice of myomectomy and surgical route was made independently of COMPARE-UF study protocols. The routes of myomectomy examined in this study included abdominal, hysteroscopic, and laparoscopic. Details about the surgery were obtained from medical records. All participant records, including pelvic imaging reports, were reviewed by a single centralized team of abstractors to ensure consistency across sites. UF details were collected from the participants' imaging reports, which included uterine dimensions and the dimensions of each UF.

Assessment of fertility and pregnancy outcomes

On annual follow-up questionnaires from 12 months through 36 months post-procedure, women were asked: "In the past year, have you had any pregnancies?" Those who responded "yes" were then asked about the number of pregnancies and the outcome of each pregnancy (up to three pregnancies), with the following response options: "pregnant and not yet delivered," "delivered a single baby," "delivered twins," "delivered triplets," "miscarriage (also known as spontaneous abortion)," "elective or therapeutic abortion," "still birth," or "tubal or ectopic pregnancy." We did not ascertain whether pregnancies were achieved with the use of assisted reproductive technologies (ART).

Assessment of covariates

We collected self-reported data on socio-demographics at baseline. And reproductive history (gravidity, parity), contraceptive history, body mass index (BMI, kg/m^2, calculated using self-reported height and weight), marital status, educational level and insurance source. Additional baseline covariate data included clinical factors, such as smoking status, co-morbid conditions (e.g., diabetes, hypertension), gynecologic conditions (sexually transmitted infections, abnormal cervical cytology, polycystic ovarian syndrome), mental health history, and history of prior medical and surgical therapies for UF. Uterine and UF characteristics at baseline, including UF size, number, and location, and uterine volume (cm^3) were derived from the pretreatment imaging reports.

On the baseline and annual follow-up questionnaires through 36 months, participants were asked about their intentions for pregnancy, specifically whether they were "trying to get pregnant now." participants completed the Patient Health Questionnaire-2, a two-item measure to screen for clinical depression; the Menopause Rating Scale, a measure of climacteric symptoms; the Uterine Fibroid Symptom (UFS)-quality of life (QOL), a disease-specific instrument that assesses symptom severity and health-related quality of life in women with UF, and the visual analog scale (VAS), which is a validated, subjective measure for acute and chronic pain (0="no pain" and 100="worst pain"). The post-procedure survey, completed within 11–18 months after the procedure, collected information about the time to resumption of usual activities, interim hospitalizations, procedural complications, and incidental cancer diagnoses.

Exclusions

We excluded participants who underwent a procedure other than myomectomy because other treatments may have been contraindicated for patients desiring future fertility, and participants who received myomectomy but had missing data on surgical route. The final analytic sample for analysis was 309 participants: 103 who underwent abdominal myomectomy, 103 who underwent hysteroscopic myomectomy, and 103 who underwent laparoscopic myomectomy.

Observation Chart

Table 1: Baseline characteristics of COMPARE-UF participants by surgical route of myomectomy

Characteristics	**Myomectomy route**			
		Laparo-scopic	**Hyster-oscopic**	**Total**
Number of women	103	103	103	309
Age (years), mean (SD)				
≤30	(15%)	(13%)	(14%)	(11%)
31–39	(60%)	(58%)	(57.0%)	(62%)
40–44	(20%)	(22%)	(23%)	(18%)
≥45	(05%)	(07%)	(06%)	(09%)
Body mass index (kg/m^2), mean (SD)	29.0 (7.1)	27.7 (7.2)	(8.9)	(7.7)
History of polycystic ovary syndrome (PCOS) Contraception to prevent pregnancy	(6.1%)	(6.2%)	(5.1%)	(5.9%)
Combined oral contraception, patch, or ring	(9.8%)	(5.5%)	(8.4%)	(7.8%)
Progestin-only implant	(4.6%)	(1.8%)	(2.9%)	(3.1%)
Progestin-only oral contraception	(5.9%)	(2.5%)	(2.2%)	(3.7%)
Hormone-containing intrauterine device	(4.9%)	(1.6%)	(2.2%)	(2.9%)
Progestin-only injectable Fertility planning status	(5.2%)	(1.8%)	(3.3%)	(3.4%)
Currently trying	(29.1%)	(28.6%)	(19.0%)	(26.4%)
Not currently trying, but within 2 years	(32.2%)	(26.7%)	(15.0%)	(25.8%)
Not currently trying, but keeping option open for future	(28.1%)	(24.0%)	(16.8%)	(23.7%)
Not currently trying, not interested in future pregnancy Parity (number of births)	(10.6%)	(20.0%)	(48.7%)	(23.8%)
0	(81.2%)	(77.2%)	(52.4%)	(72.4%)
1	(11.9%)	(14.3%)	(15.8%)	(13.8%)
≥2	(7.0%)	(8.5%)	(31.9%)	(13.8%)
History of difficulty conceiving ***Fibroid characteristics*** Number of prior fibroid procedures	(27.1%)	(28.0%)	(25.2%)	(27.0%)
0	(81.7%)	(85.5%)	(78.8%)	(82.5%)
1	(17.0%)	(12.0%)	(18.0%)	(15.3%)
≥2	(1.3%)	(2.5%)	(43.3%)	(2.3%)
Uterine volume (cm^3), mean (SD)	(737)	(390)	(275)	(585)
Maximum fibroid volume (cm^3), mean (SD) Any submucous fibroid	(743.4)	(313.6)	(425.9)	(552.2)
Yes	(27.1%)	(22.1%)	(63.0%)	(34.1%)

Table 2: Cumulative probability of pregnancy and live birth during follow-up, by myomectomy route[a]

Characteristic		**Abdominal**	**Laparoscopic**	**Hysteroscopic**	**Total**
		103	**103**	**103**	**309**
Myomectomy Route	**Subgroup**	**Pregnancies/ Total women (%) = 68**	**Probability of pregnancy (95% CI) by follow-up time**		
			12 months	**24 months**	**36 months**
Abdominal	All women	25(08%)	0.13 (0.08–0.14)	0.20 (0.16–0.25)	0.24 (0.19–0.30)
Hysteroscopic	All women	23(07%)	0.16 (0.11–0.22)	0.24 (0.17–0.32)	0.33 (0.23–0.45)
Laparoscopic	All women	20(06%)	0.16 (0.13–0.19)	0.24 (0.20–0.29)	0.27 (0.23–0.34)
Myomectomy Route	**Subgroup**	**Live births/ Total women (%) =39**	**Probability of live birth (95% CI) by follow-up time**		
			12 months	**24 months**	**36 months**
Abdominal	All women	14 (04.5%)	0.01 (0.00–0.05)	0.10 (0.06–0.17)	0.10 (0.06–0.17)
Hysteroscopic	All women	13 (04.2%)	0.04 (0.02–0.08)	0.13 (0.08–0.21)	0.19 (0.12–0.30)
Laparoscopic	All women	12 (03.8%)	0.02 (0.01–0.05)	0.12 (0.08–0.17)	0.14 (0.10– 0.21)

Abbreviations: CI=confidence interval.

- Cumulative probability accounts for censoring using life-table methods and adjusts for confounding using propensity score weights.
- Based on self-report at baseline only.

Results

Baseline socio-demographic and clinical characteristics

There were no appreciable differences in the percentages lost to follow-up by myomectomy group. Participants who underwent abdominal myomectomy tended to be younger, nulliparous, have larger uterine volume at surgery and larger maximum UF volume. women who underwent other routes of myomectomy. They were also more likely to be currently trying (29.1%) or planning to try to conceive within the next two years (32.3%), relative to the other routes of myomectomy. Hysteroscopic myomectomy patients were substantially more likely than the other two myomectomy groups to have 2 or more prior UF procedures. There was little difference in history of infertility across the three groups

Probabilities of pregnancy and live birth, overall and by myomectomy route

Among 309 women who underwent myomectomy, 68 reported pregnancy and 39 reported live birth during follow-up; some of these women were still pregnant at the end of follow-up. There was no appreciable difference in the probability of pregnancy or live birth by route of myomectomy overall, among women intending pregnancy within 2 years, or among women actively trying to conceive.

Among women who had a myomectomy, the strongest predictors of reported conception were age and pregnancy intent at baseline (data not shown). After three years, those respective cumulative probabilities of pregnancy increased to: 0.67 (95% CI: 0.48–0.79), 0.57 (95% CI: 0.47–0.65), 0.34 (95% CI: 0.21– 0.45), and 0.30 (95% CI: 0.08–0.47). This statistical model had a Harrell's C-index of 0.80 (55), indicating very good prediction. Other variables in this model that did not appreciably improve prediction included: myomectomy route, use of contraception at baseline, number of prior UF procedures, parity, and infertility history.

Statistical analysis: We assessed prospectively the association between surgical route for myomectomy (abdominal, hysteroscopic, laparoscopic) and self-reported pregnancy and live birth in each 12-month interval during 36 months of follow-up**.** First, we used life-table methods with propensity score weighting to estimate the probabilities of pregnancy and live birth and 95% confidence intervals (CIs) in each time interval (0–12 months, 0–24 months, or 0–36 months), after accounting for censoring. Women were censored at the first occurrence of any of the following events: report of natural or surgical menopause, loss to follow-up, or end of follow-up (36 months). Potential correlation between patients from the same clinical center was handled by fitting a robust empirical variance estimator, with clustering by clinical center.

We performed sensitivity analyses that excluded women with hysteroscopic myomectomy as a comparison group, owing to the large differences in patient and UF characteristics between these women and all other participants. This involved re-running the propensity score weighting to balance the UF characteristics across the abdominal and laparoscopic myomectomy groups, the life-table analyses, and logistic regression models for associations with pregnancy and livebirth. A subsequent sensitivity analysis was conducted to account for additional UF characteristics: maximum UF volume and submucous location. These variables were not included in the primary propensity model because their method of collection was not standardized across clinical sites and they were thought to be captured less accurately than uterine volume.

Discussion

In this prospective analysis of COMPARE-UF participants undergoing myomectomy for symptomatic UF, there was little association between surgical route for myomectomy and the probability of conception or livebirth during a 36-month follow-up period, after adjusting for patient demographics, reproductive history, and uterine volume. Among myomectomy patients, the strongest predictors of pregnancy success were age and pregnancy intent at baseline. Among women who reported currently trying to conceive at baseline, the cumulative probabilities of pregnancy during three years of follow-up, after accounting for age and pregnancy intent, myomectomy route was not an important predictor of pregnancy. These results contribute to the sparse literature on the influence of surgical route of myomectomy and fertility outcomes.

Large differences in pre-treatment patient characteristics were observed across the different routes of myomectomy. These differences are not surprising given that procedures like abdominal myomectomy are typically recommended for women with larger uterine volumes, and larger and more numerous UF. Although we successfully adjusted for many of the observed differences using propensity weighting, this approach includes assumptions that may not fully capture the severity of UF characteristics among women who underwent abdominal myomectomy (e.g., setting mean uterine volume to 300 cm^3 for all subtypes of myomectomy, even though the mean volume for all women with abdominal myomectomy was ~900 cm^3). To increase the generalizability of our findings, we repeated our analyses after excluding women with hysteroscopic myomectomy, for whom UF disease severity would be lower relative to women undergoing abdominal or laparoscopic myomectomy. The analyses restricted to abdominal and laparoscopic myomectomy focused on treatments with better covariate overlap. Such a comparison would better emulate the real-life situation where a given patient might be eligible for abdominal or laparoscopic myomectomy, but not hysteroscopic myomectomy. Again, these results showed little evidence for a difference in pregnancy or live birth comparing abdominal and laparoscopic myomectomy surgical routes. Thus, our results indicate that the choice of abdominal vs. laparoscopic myomectomy for women with UF that cannot be appropriately treated via the hysteroscopic route can be based on other considerations besides future fertility.

Limitations of the study include the restriction of analyses to women undergoing myomectomy only and potential unmeasured differences in the distribution of uterine anatomy characteristics across myomectomy procedures, which could have introduced residual confounding by indication. However, sensitivity analyses that included additional UF characteristics in the propensity score (e.g., location and size of largest UF) had little impact on the results. To the extent that confounding was not properly accounted for, we might expect lower fertility success among women undergoing abdominal myomectomy relative to the other types of myomectomy because women offered abdominal myomectomy tend to have more severe disease (e.g., larger and more numerous UF; submucous UF which could be more strongly associated with inhibition of implantation) (7, 8). Many of the demographic characteristics that are more common among women with severe UF (e.g., later reproductive age, African ancestry) are also risk factors for adverse reproductive outcomes such as infertility and spontaneous abortion (18, 19), and could confound the potential association between myomectomy route and these outcomes (7). This, in turn, limits our ability to compare fertility across different treatments. As mentioned above, propensity weighting may have made the results less generalizable to women with more severe UF who undergo abdominal myomectomy. Whether it is even appropriate to compare abdominal with laparoscopic and hysteroscopic myomectomy is debatable given a single patient may never be offered all three of these options. However, the extent to which differences in pre-operative uterine anatomy or other UF characteristics alone, independent of route of procedure, would have had a direct effect on fertility outcomes is unclear. Lack of data on specific types of reproductive failures such as fertilization, implantation, or post-implantation losses precluded the examination of potential mechanisms. We did not have data on whether women used fertility treatments to conceive or whether they conceived spontaneously, and differences in these factors may have obscured differences in fertility success among the surgical routes for myomectomy.

The COMPARE-UF data were collected from a convenience sample of patients undergoing UF procedures at 10 clinical sites across the U.S.; thus, the prevalence of myomectomy subtypes in this population is not representative of the general population. The primary eligibility criterion for inclusion in the COMPARE-UF registry was the presence of symptomatic UF, including subfertility as a syndrome. The proportion of women undergoing hysteroscopic resection reflects the distribution of women with UF suitable for hysteroscopic resection among our study population, the majority of whom were not actively trying to get pregnant. We also note that live birth rates were partly limited by varying lengths of follow-up. If patients were advised to wait 4–6 months post-procedure before attempting to conceive and had average fecundability, the first births would not take place until after 12 months of follow-up.

Another important limitation is that we relied on clinical imaging and operative reports at participating clinical sites to characterize the location of the UF being removed. Though reports were abstracted using a standard form that included data on FIGO stage, fewer than 2% of COMPARE-UF reports used the FIGO classification. The general categorization of UF into submucous, intramural, and subserosal has been in practice for several decades, and there is some clinical and some basic science evidence to indicate that submucous UF are more likely to contribute to infertility given their ability to cause uterine cavity distortion . There is also evidence that removal of submucous UF increases subsequent pregnancy rates. However, controversy remains about the role of intramural UF in the pathogenesis of infertility . In a recently-published debate, experts cited several mechanisms by which intramural UF could influence fertility, including impaired endometrial and myometrial blood supply, reduced endometrial receptivity, greater myometrial contractility, thickening of the UF capsule, and hormonal and genetic alterations, all of which favoured removal of intramural UF to improve fertility. Other experts argued against removal of intramural UF to improve fertility, citing concerns about surgical complications and challenges in the interpretation of published studies due to methodologic issues such as confounding, biologic heterogeneity (e.g., driver mutations; FIGO type 3 vs. 4), and selection bias related to differential referral patterns and insurance coverage for UF care (65–68). Conversely, there is general agreement that subserosal UF have limited, if any, impact on fertility although data are also limited, particularly for larger UF (11). Finally, comparing fertility in women with intramural UF surrounded by myometrium (FIGO type 4) with those that contact the endometrium (FIGO type 3) is a novel area of investigation, but was beyond the scope of this report.

There is no significant difference in the chances of conception or delivering a live baby by the various myomectomy routes. Results from the present study indicate that there is no difference in the probability of pregnancy or live birth during 36 months of follow-up according to surgical route of myomectomy, particularly when comparing abdominal vs. laparoscopic routes, after accounting for pre-treatment differences in patient characteristics. Additional follow-up may be needed to determine if the similarity in fertility outcomes across myomectomy groups persists over time. If confirmed, our results provide little reason for change in how current myomectomy route is chosen by patients in consultation with their providers regarding a patient's desire for future fertility.

Conclusion:

There is no significant difference in the chances of conception or delivering a live baby by the various myomectomy routes.

Declarations:

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