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Route of myomectomy and fertility: a prospective cohort study

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Objective: To assess prospectively the association between the myomectomy route and fertility.
Design: Prospective cohort study.
Setting: The Comparing Treatments Options for Uterine Fibroids (COMPARE-UF) Study is a multisite national registry of eight clinic centers across the United States.
Patient(s): Reproductive-aged women undergoing surgery for symptomatic uterine fibroids.
Intervention(s): Not applicable.
Main Outcome Measure(s): We used life-table methods to estimate cumulative probabilities and 95% confidence intervals (CI) of pregnancy and live birth by the myomectomy route during 12, 24, and 36 months of follow-up (2015–2019). We also conducted 12-month interval-based analyses that used logistic regression to estimate odds ratios and 95% CIs for associations of interest. In all analyses, we used propensity score weighting to adjust for differences across surgical routes.
Result(s): Among 1,095 women who underwent myomectomy (abdominal = 388, hysteroscopic = 273, and laparoscopic = 434), 202 reported pregnancy and 91 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 1.28 (95% CI, 0.76–2.14) for hysteroscopic myomectomy and 1.19 (95% CI, 0.76–1.85) for laparoscopic myomectomy compared with abdominal myomectomy. Among women intending pregnancy, adjusted ORs were 1.27 (95% CI, 0.72–2.23) for hysteroscopic myomectomy and 1.26 (95% CI, 0.77–2.04) for laparoscopic myomectomy compared with abdominal myomectomy. Associations were slightly stronger but less precise for live birth.
Conclusion(s): The probability of conception or live birth did not differ appreciably by the myomectomy route among women observed for 36 months postoperatively.

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Uterine fibroids (UFs) are the leading indication for hysterectomy in the United States (1, 2) and account for more than $2.2 billion annually in health care costs (3). Although the lifetime cumulative incidence of clinical diagnosis is approximately 30%, data from the standardized screening of women aged 35–49 years estimated a cumulative incidence of ultrasound-detectable UFs by age 50 of >70% (4). Studies show a greater burden of UFs among Black than white women, with disproportionately higher incidence, earlier ages at diagnosis and surgery, and more severe symptoms at the time of initial diagnosis (4–7). Uterine fibroid symptoms include heavy menstrual bleeding, anemia, pain, pelvic pressure, and genitourinary symptoms. The peak incidence for UF symptoms occurs during the reproductive years (7, 8) when many women are attempting pregnancy. Given that Black women tend to experience earlier onset of UFs and more severe disease, the impact of UFs on their fertility may be greater.

Depending on their location within the uterus, UFs may be associated with impaired fertility (9–12). However, studies of UFs and fertility are inconsistent, and the association may be due in part to uncontrolled or residual confounding (e.g., by age), referral bias (13), or detection bias (7, 14). Approximately 10% of pregnant women have detectable UFs in the first trimester (15), and UF presence has been associated with spontaneous abortion in some (16, 17) but not all studies (18). Furthermore, treatments for UFs may affect fertility via adverse sequelae. In the United States, health insurance typically covers UF treatment but not infertility treatment; thus, UF treatment to improve fertility is likely overused. However, research investigating the extent to which fertility outcomes differ based on the route of myomectomy is limited (19–22).

Myomectomy, the most common uterine-preserving procedure performed for UFs in the United States (23–30), accounts for approximately 22% of all UF surgeries (30). Considering inpatient and outpatient procedures in the United States, the most common surgical route for myomectomy is abdominal (via laparotomy; >75%), followed by laparoscopic (with or without robotic assistance) (approximately 15%) and hysteroscopic (approximately 10%) routes (20, 30–33). According to data from the American College of Surgeons National Surgical Quality Improvement Program database, the percentage of abdominal myomectomies increased by 11 percentage points from 2012 to 2016 (while laparoscopic myomectomy decreased), likely because of concerns about morcellation and cancer (32, 34). Compared with laparoscopic myomectomy, abdominal myomectomy has been associated with longer hospitalizations, higher readmission rates, and greater morbidity (31, 32).

Abdominal myomectomy tends to be recommended more commonly for patients who have larger uterine volume, multiple UFs, and UFs 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 UFs (31). Hysteroscopic myomectomy is recommended for patients with symptomatic submucous UFs. A 2020 review of surgical treatment of UFs for subfertility, including four randomized controlled trials with 442 participants, concluded that there was very low-quality evidence on the association between surgical approach for myomectomy and subsequent subfertility overall and by UF location (20). Observational studies also have been limited by small sample size, retrospective study design (which may be prone to selection bias), inconsistency of results across studies, and examination of only one type of surgical route (11–13, 16, 19–21, 31, 35–45).

Prospective cohort studies that compare fertility success across surgical approaches for myomectomy can fill important gaps in the literature. In this report, we prospectively examine the association between the route of myomectomy (abdominal, hysteroscopic, and laparoscopic) for UFs 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 the 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 (COMPARE-UF) Study is a multisite national registry of women who were scheduled for treatment for symptomatic fibroids at 1 of 8 clinic centers across the United States (NCT02260752, clinicaltrials.gov): Mayo Clinic, INOVA Health System, Brigham and Women's Hospital, the University of Mississippi Medical Center, the University of California Fibroid Network, Henry Ford Health System, the University of Michigan, and the University of North Carolina between 2015 and 2019. Duke Clinical Research Institute (DCRI) served as the Research Data and Coordinating Center. 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 previously (46). The registry protocol was reviewed and approved by the Duke Institutional Review Board for the coordinating center and by the review boards at each of the clinical recruitment sites.

Trained site coordinators screened all women for eligibility. Eligible participants then provided informed consent and Health Insurance Portability and Accountability Act authorization, and completed an online baseline questionnaire through a secure, password-protected, web-based study portal (SignalPath, LLC, Durham, NC) or through paper or phone interviews with clinical site coordinators. The baseline questionnaire elicited self-reported data on patient sociodemographics, medical history, fibroid history, prior fibroid procedures, current and prior fibroid therapies, reproductive history, measures of financial distress, and childbearing plans. Per protocol, the baseline questionnaire was completed within the 30-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 Research Call Center at the DCRI. The DCRI sent reminders to the participants to complete the questionnaires. If a participant was lost to follow-up, coordinators at both the DCRI 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 the 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. Uterine fibroids 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 12–36 months postprocedure, 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 3 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," "stillbirth," or "tubal or ectopic pregnancy." We did not ascertain whether pregnancies were achieved with the use of assisted reproductive technologies.

Assessment of Covariates

We collected self-reported data on sociodemographics at baseline. These factors included age, self-identified race ("How would you best describe your race?" with response options: Black/African American, Asian, American Indian/ Alaska Native, Native Hawaiian/Pacific Islander, White, other), ethnicity (Hispanic/Latina, non-Hispanic Latina), reproductive history (gravidity, parity), contraceptive history, body mass index (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, comorbid 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 UFs. Uterine and UF characteristics at baseline, including UF size, number, 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." If not, women were asked, "Are you planning to become pregnant in the future?" with response options of "Yes, likely within the next 2 years," "Would like to keep as an option," and "No." To ascertain infertility history, the baseline questionnaire included the question: "Did you ever try for more than one year to get pregnant?" All follow-up questionnaires included the question: "Have you been trying to get pregnant for a year or more?" At all time points (baseline and follow-up), participants completed the Patient Health Questionnaire-2, a two-item measure to screen for clinical depression (47, 48); the Menopause Rating Scale, a measure of climacteric symptoms (49, 50); the UF Symptom-quality of life, a disease-specific instrument that assesses symptom severity and health-related quality of life in women with UFs (51), and the visual analog scale, which is a validated, subjective measure for acute and chronic pain (0 = "no pain" and 100 = "worst pain"). The postprocedure 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

The present analysis included all COMPARE-UF eligible patients enrolled from December 28, 2015 through December 17, 2019. We excluded participants who underwent a procedure other than myomectomy because other treatments may have been contraindicated for patients desiring future fertility. Furthermore, we excluded participants who received myomectomy but had missing data on the surgical route (Supplemental Figure 1, available online). The final analytic sample for analysis was 1,095 participants: 388 who underwent abdominal myomectomy, 273 who underwent hysteroscopic myomectomy, and 434 who underwent laparoscopic myomectomy.

All sites recruited women in each of these groups, with the site-specific myomectomy percentages ranging from 19.2%

(University of Mississippi Medical Center) to 71.7% (University of California Fibroid Network).

Statistical Analysis

We assessed prospectively the association between the 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 (2015–2019). We compared sociodemographic and clinical factors between the myomectomy surgical route groups. Our primary events of interest were the time from index procedure to the occurrence of first pregnancy and first live birth during the follow-up period. Time was measured as 12, 24, or 36 months corresponding to first, second, or third annual follow-up, respectively. Because of the observational design of COMPARE, we used inverse propensity weighting methods, specifically overlap weighting, to adjust for confounding (52, 53). The propensity score (probability of surgical route for myomectomy) was estimated using a multinomial regression model with the myomectomy route as the dependent variable and participant characteristics considered to be potential confounders as independent variables. Potential confounders for inclusion in the propensity model were identified a priori based on a review of the literature, clinical experience, and the drawing of a causal diagram. These included age, race/ethnicity, number of prior UF procedures, body mass index, history of polycystic ovary syndrome, contraception (combined oral contraception, progestin-only oral contraception, patch, vaginal ring, implant, hormone-containing intrauterine device, progestin-only injectable), number of children (0, 1, ≥ 2), fertility intent (currently trying; not currently trying but intending to try within 2 years; not currently trying but intending to try in the future; not interested in future pregnancy), history of difficulty becoming pregnant, and uterine volume. In sensitivity analyses, we further adjusted for the largest UF volume and UFs with a submucous location. We did not consider the "number of UF" in the propensity score because of incomplete data on this variable. Covariates with missing data at baseline were imputed using the fully conditional specification method in SAS PROC MI (54), using all patient-reported variables available in the COMPARE-UF database (46). Given the low percentage of missing data for any given covariate (<5%), we used a single imputation data set in this analysis, consistent with previous publications from this registry and prior sensitivity analyses that showed no difference using multiple imputation.

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). We then conducted a 12-month interval-based analysis that updated pregnancy intent annually and used logistic regression to estimate odds ratios (ORs) and 95% CIs for the association between myomectomy routes and annual outcomes of conception and live birth. The unit of analysis was study time (person-years). The analysis pooled results across all intervals. We included a fixed effect for treatment and used propensity score weighting to create comparable groups by the procedure. In addition, we repeated analyses in subgroups restricted by pregnancy intent: actively trying to conceive or intending to conceive within the next 2 years. Potential correlation between patients from the same clinical center was handled by fitting a robust empirical variance estimator, with clustering by the 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 participants and all other participants. This involved rerunning 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 live birth. We conducted a subsequent sensitivity analysis 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. All analyses were conducted using SAS software (SAS Institute, Cary, NC).

RESULTS

Baseline Sociodemographic and Clinical Characteristics

There were no appreciable differences in the percentages lost to follow-up by the myomectomy group (data not shown). Participants who underwent abdominal myomectomy tended to be younger, nulliparous, have a larger uterine volume at surgery, larger maximum UF volume, and were more likely to identify as Black or African American than women who underwent other routes of myomectomy (Table 1). Participants who underwent abdominal myomectomy were also more likely to be currently trying (29.1%) or intending to conceive within the next 2 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 prior UF procedures. There was little difference in the history of infertility across the 3 groups. Likewise, the groups were not notably different with respect to UF Symptom-quality of life (UFS-QOL), EuroQOL scale, or visual analog scale scores. Comparability between the treatment groups was achieved at baseline after propensity weighting (data not shown).

Probabilities of Pregnancy and Live Birth, Overall and by Myomectomy Route

Among 1,095 women who underwent myomectomy, 202 reported pregnancy, and 91 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 the route of myomectomy

TABLE 1

Baseline characteristics of COMPARE-UF participants by surgical route of myomectomy.

	Myomectomy route			
Characteristic	**Abdominal**	**Laparoscopic**	**Hysteroscopic**	**Total**
No. of women	388	434	273	1,095
Age (years), mean (SD)	36.8 (5.7)	37.3 (5.9)	40.9 (7.2)	38.0 (6.4)
≤30	49 (12.6%)	53 (12.2%)	25 (9.2%)	127 (11.6%)
31–39	218 (56.2%)	227 (52.3%)	88 (32.2%)	533 (48.7%)
40–44	85 (21.9%)	103 (23.7%)	73 (26.7%)	261 (23.8%)
≥45	36 (9.3%)	51 (11.8%)	87 (31.9%)	174 (15.9%)
Race				
Black or African American	198 (51.0%)	154 (35.8%)	104 (38.2%)	456 (41.8%)
White	118 (30.4%)	188 (43.7%)	127 (46.7%)	433 (39.7%)
Other	72 (18.6%)	88 (20.5%)	41 (15.1%)	201 (18.4%)
Hispanic or Latina	27 (7.0%)	21 (5.0%)	29 (10.9%)	77 (7.2%)
Body mass index (kg/m^2), mean (SD)	29.0 (7.1)	27.7 (7.2)	30.0 (8.9)	28.7 (7.7)
History of polycystic ovary syndrome	23 (6.1%)	26 (6.2%)	14 (5.1%)	63 (5.9%)
Contraception to prevent pregnancy				
Combined oral contraception, patch, or ring	38 (9.8%)	24 (5.5%)	23 (8.4%)	85 (7.8%)
Progestin-only implant	18 (4.6%)	8 (1.8%)	8 (2.9%)	34 (3.1%)
Progestin-only oral contraception	23 (5.9%)	11 (2.5%)	6 (2.2%)	40 (3.7%)
Hormone-containing intrauterine device	19 (4.9%)	7 (1.6%)	6 (2.2%)	32 (2.9%)
Progestin-only injectable	20 (5.2%)	8 (1.8%)	9 (3.3%)	37 (3.4%)
Fertility planning status				
Currently trying	113 (29.1%)	124 (28.6%)	52 (19.0%)	289 (26.4%)
Not currently trying, but within 2 years	125 (32.2%)	116 (26.7%)	41 (15.0%)	282 (25.8%)
Not currently trying, but keeping option open for future	109 (28.1%)	104 (24.0%)	46 (16.8%)	259 (23.7%)
Not currently trying, not interested in future pregnancy	41 (10.6%)	87 (20.0%)	133 (48.7%)	261 (23.8%)
Parity (no. of births)				
0	315 (81.2%)	335 (77.2%)	143 (52.4%)	793 (72.4%)
1	46 (11.9%)	62 (14.3%)	43 (15.8%)	151 (13.8%)
≥2	27 (7.0%)	37 (8.5%)	87 (31.9%)	151 (13.8%)
History of difficulty conceiving	101 (27.1%)	117 (28.0%)	68 (25.2%)	286 (27.0%)
Fibroid characteristics:				
No. of prior fibroid procedures				
0	317 (81.7%)	371 (85.5%)	215 (78.8%)	903 (82.5%)
1	66 (17.0%)	52 (12.0%)	49 (18.0%)	167 (15.3%)
≥2	5 (1.3%)	11 (2.5%)	9 (43.3%)	25 (2.3%)
Uterine volume (cm^3), mean (SD)	912.8 (737)	486.4 (390)	265.6 (275)	580.5 (585)
Maximum fibroid volume (cm^3), mean (SD)	483.5 (743.4)	265.3 (313.6)	72.9 (425.9)	295.2 (552.2)
Any submucous fibroid				
Yes	105 (27.1%)	96 (22.1%)	172 (63.0%)	373 (34.1%)
No/missing[a]	283 (72.9%)	338 (77.9%)	101 (37.0%)	722 (65.9%)
UFS-QOL, mean (SD)				
Concern	47.1 (32.2)	52.6 (33.9)	37.2 (28.4)	46.8 (32.6)
Activities	52.7 (28.8)	56.3 (29.2)	50.0 (29.1)	53.5 (29.1)
Energy/mood	50.3 (27.7)	52.8 (28.3)	49.2 (27.9)	51.0 (28.0)
Control	48.7 (27.0)	51.7 (27.6)	48.8 (26.8)	49.9 (27.2)
Self-conscious	39.8 (31.6)	50.2 (31.6)	52.7 (32.7)	47.3 (32.3)
Sexual function	54.3 (34.8)	55.9 (33.7)	49.8 (35.7)	53.8 (34.7)
Total summary of 6 subscale scores above	49.5 (25.8)	53.4 (25.9)	47.3 (26.0)	50.6 (26.0)
Symptom severity	51.6 (25.6)	48.6 (23.9)	54.4 (24.6)	51.1 (24.8)
EQ-5-Dimension Scale (% without problems)				
Mobility	314 (81.6%)	378 (87.7%)	228 (83.8%)	920 (84.6%)
Self-care	365 (95.1%)	416 (96.7%)	255 (93.4%)	1036 (95.3%)
Usual activities	250 (65.1%)	287 (66.9%)	192 (70.3%)	729 (67.1%)
Pain/discomfort	80 (20.8%)	108 (25.1%)	101 (37.0%)	289 (26.5%)
Anxiety/depression	156 (40.7%)	163 (38.0%)	112 (41.2%)	431 (39.8%)
Visual analog pain scale (0–100), mean (SD)	72.5 (19.9)	74.7 (16.7)	73.3 (18.2)	73.6 (18.3)

UFS-QOL = Uterine Fibroid Symptom and Quality of Life subscale, EQ = EuroQOL scale.
[a] Unable to distinguish "no" from "missing" because of lack of standardization and inconsistent reporting of imaging data across clinical sites.

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overall, among women intending pregnancy within 2 years or among women actively trying to conceive (Table 2).

Among women who had a myomectomy, the strongest predictors of reported conception were age and pregnancy intent at baseline (data not shown). Among women who reported currently trying to conceive at baseline, the cumulative probabilities of pregnancy within the first year of follow-up for women aged ≤30, 31–39, 40–44, and ≥45 years were: 0.37 (95% CI, 0.24–0.47), 0.29 (95% CI, 0.23–0.35), 0.16 (95% CI, 0.09–0.22), and 0.14 (95% CI, 0.03–0.23). After 3 years,

TABLE 2

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

Myomectomy Route	Subgroup	Pregnancies/total women (%)	Probability of pregnancy (95% CI) by follow-up time		
			12 months	24 months	36 months
Abdominal	All women	69/388 (17.8%)	0.13 (0.08–0.14)	0.20 (0.16–0.25)	0.24 (0.19–0.30)
	Trying to conceive or intending to conceive within the next 2 years[b]	64/238 (26.9%)	0.25 (0.17–0.34)	0.37 (0.27–0.48)	0.45 (0.33–0.59)
	Trying to conceive[b]	36/113 (31.9%)	0.28 (0.18–0.42)	0.41 (0.28–0.57)	0.47 (0.30–0.66)
Hysteroscopic	All women	37/273 (13.6%)	0.16 (0.11–0.22)	0.24 (0.17–0.32)	0.33 (0.23–0.45)
	Trying to conceive or intending to conceive within the next 2 years[b]	34/94 (36.2%)	0.26 (0.17–0.38)	0.41 (0.29–0.55)	0.56 (0.40–0.74)
	Trying to conceive[b]	22/53 (41.5%)	0.36 (0.24–0.53)	0.48 (0.33–0.66)	0.63 (0.42–0.83)
Laparoscopic	All women	96/434 (22.1%)	0.16 (0.13–0.19)	0.24 (0.20–0.29)	0.27 (0.23–0.34)
	Trying to conceive or intending to conceive within the next 2 years[b]	88/241 (36.5%)	0.28 (0.21–0.35)	0.40 (0.32–0.49)	0.50 (0.38–0.62)
	Trying to conceive[b]	60/125 (48.0%)	0.40 (0.30–0.52)	0.54 (0.42–0.67)	0.67 (0.50–0.83)
Myomectomy Route	**Subgroup**	**Live births/total women (%)**	**Probability of live birth (95% CI) by follow-up time**		
			12 months	**24 months**	**36 months**
Abdominal	All women	28/388 (7.2%)	0.01 (0.00–0.05)	0.10 (0.06–0.17)	0.10 (0.06–0.17)
	Trying to conceive or intending to conceive within the next 2 years[b]	26/238 (10.9%)	0.01 (0.00–0.07)	0.20 (0.12–0.32)	0.20 (0.12–0.32)
	Trying to conceive[b]	16/113 (14.2%)	0.02 (0.00–0.12)	0.25 (0.14–0.43)	0.25 (0.14–0.43)
Hysteroscopic	All women	19/273 (7.0%)	0.04 (0.02–0.08)	0.13 (0.08–0.21)	0.19 (0.12–0.30)
	Trying to conceive or intending to conceive within the next 2 years[b]	17/94 (18.1%)	0.05 (0.02–0.14)	0.21 (0.12–0.35)	0.31 (0.18–0.50)
	Trying to conceive[b]	10/53 (18.9%)	0.06 (0.02–0.19)	0.27 (0.14–0.48)	0.30 (0.16–0.52)
Laparoscopic	All women	44/434 (10.1%)	0.02 (0.01–0.05)	0.12 (0.08–0.17)	0.14 (0.10– 0.21)
	Trying to conceive or intending to conceive within the next 2 years[b]	39/241 (16.2%)	0.03 (0.01–0.08)	0.20 (0.13–0.29)	0.25 (0.16–0.37)
	Trying to conceive[b]	22/125 (17.6%)	0.03 (0.01–0.10)	0.26 (0.15–0.41)	N/A (no data)

CI = confidence interval.
[a] Cumulative probability accounts for censoring using life-table methods and adjusts for confounding using propensity score weights.
[b] Based on self-report at baseline only.

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TABLE 3

Myomectomy route in relation to pregnancy and live birth, interval-based analysis.

Myomectomy route	All women: No. of events/total (%)	Unadjusted: OR	Unadjusted: 95% CI	Adjusted[a]: OR	Adjusted[a]: 95% CI	Adjusted and restricted to women with pregnancy intent[a,b]: OR	Adjusted and restricted to women with pregnancy intent[a,b]: 95% CI
Pregnancy							
Abdominal	69/388 (17.8%)	1.00	Reference	1.00	Reference	1.00	Reference
Hysteroscopic	37/273 (13.6%)	0.81	0.52, 1.24	1.28	0.76, 2.14	1.27	0.72, 2.23
Laparoscopic	96/434 (22.1%)	1.38	0.98, 1.94	1.19	0.76, 1.85	1.26	0.77, 2.04
Live birth							
Abdominal	28/388 (7.2%)	1.00	Reference	1.00	Reference	1.00	Reference
Hysteroscopic	19/273 (7.0%)	1.03	0.57, 1.86	1.66	0.80, 3.43	1.71	0.81, 3.65
Laparoscopic	44/434 (10.1%)	1.47	0.90, 2.39	1.38	0.72, 2.62	1.49	0.77, 2.89

Abbreviations: OR = odds ratio, CI = confidence interval.
[a] Applies propensity score weights to account for differences in demographics, symptoms, and fibroid characteristics.
[b] Restricted to women with fertility intent (actively trying to conceive or intending to conceive within the next 2 years) at the beginning of the 12-month interval (time-varying covariate).

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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.

ORs of Pregnancy and Live Birth, by Myomectomy Route

Overall, adjusted ORs for pregnancy were 1.28 (95% CI, 0.76–2.14) for hysteroscopic myomectomy and 1.19 (95% CI, 0.76–1.85) for laparoscopic myomectomy compared with abdominal myomectomy (Table 3). There was evidence of substantial confounding by patient and UF characteristics, as evidenced by the attenuation of unadjusted ORs after adjustment for confounding using propensity weighting.

Among women intending pregnancy, ORs were 1.27 (95% CI, 0.72–2.23) for hysteroscopic myomectomy and 1.26 (95% CI, 0.77–2.04) for laparoscopic myomectomy compared with abdominal myomectomy. Associations were stronger but less precise for live birth.

When we repeated analyses after excluding women with hysteroscopic myomectomy and derived new propensity weights to account for patient and UF differences across laparoscopic vs. abdominal myomectomy, the results were similar when comparing these two surgical approaches (Table 4). Additional adjustment for maximum UF size and submucous UFs also yielded consistent findings (Table 4).

DISCUSSION

In this prospective analysis of COMPARE-UF participants undergoing myomectomy for symptomatic UFs, there was little association between the surgical route for myomectomy and the probability of conception during a 36-month follow-up period, after adjusting for patient demographics, reproductive history, and uterine volume. Associations with live birth were stronger but less precise due to small numbers. 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 3 years of follow-up, after accounting for

TABLE 4

Myomectomy route (laparoscopic vs. abdominal) in relation to pregnancy and live birth during follow-up, interval-based analysis.

Myomectomy route	Unadjusted: OR	Unadjusted: 95% CI	Adjusted[a]: OR	Adjusted[a]: 95% CI	Adjusted[a]: OR[c]	Adjusted[a]: 95% CI[c]	Restricted to pregnancy intent[a,b]: OR	Restricted to pregnancy intent[a,b]: 95% CI	Restricted to pregnancy intent[a,b]: OR[c]	Restricted to pregnancy intent[a,b]: 95% CI[c]
Pregnancy										
Abdominal	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Laparoscopic	1.38	0.98, 1.94	1.15	0.81, 1.66	1.14	0.79, 1.64	1.25	0.85, 1.84	1.25	0.84, 1.84
Live birth										
Abdominal	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Laparoscopic	1.47	0.90, 2.39	1.32	0.79, 2.19	1.24	0.75, 2.06	1.42	0.84, 2.39	1.35	0.80, 2.25

Abbreviations: OR = odds ratio, CI = confidence interval.
[a] Applies propensity score weights to account for differences in demographics, symptoms, and fibroid characteristics.
[b] Restricted to women with fertility intent (actively trying to conceive or intending to conceive within the next 2 years) at the beginning of the 12-month interval (time-varying covariate).
[c] Propensity score weights augmented by maximum fibroid volume and the presence of at least one submucous fibroid.

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varying lengths of follow-up using life-table methods, were as high as 67% among women aged 30 or younger and 30% among women aged $\geq$45 years. The model with age and pregnancy intent showed excellent predictive probability for pregnancy (80%); after accounting for age and pregnancy intent, the myomectomy route was not an important predictor of pregnancy. These results contribute to the sparse literature on the influence of the surgical route of myomectomy and fertility outcomes.

Large differences in pretreatment 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 UFs. 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 the mean uterine volume to 300 cm^3 for all subtypes of myomectomy, even though the mean volume for all women with abdominal myomectomy was approximately 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 comparing abdominal and laparoscopic myomectomy surgical routes. Thus, our results indicated that the choice of abdominal vs. laparoscopic myomectomy for women with UFs that cannot be treated appropriately via the hysteroscopic route can be based on other considerations besides future fertility.

Although myomectomy is the treatment of choice for women desiring to preserve their fertility (24–29) and is performed frequently among women with unexplained infertility or recurrent spontaneous abortion, its effect on subsequent fertility is unclear (11–13, 16, 20, 21, 35–43). One study reported that the surgical route of myomectomy had little effect on fertility outcomes (44), but other studies have not directly compared the surgical routes of myomectomy (19, 31, 45). One difficulty in comparing outcomes in nonrandomized participants is that important factors associated with pregnancy outcomes, particularly age and UF characteristics, may differ between groups before treatment (56, 57). For example, a recent study reported that women with >6 UFs removed were less likely to conceive; however, it was unclear whether this was related to the severity of UFs itself or to the surgical procedure (19). Moreover, nonpatient factors, including the skill of the surgeon and the availability and/or use of assisted reproductive technology after UF treatment may have influenced study outcomes as well.

The strengths of the analysis include the prospective design, 3-year follow-up period, relatively large sample size, availability of pretreatment medical and operative notes, detailed covariate information, and application of validated propensity weighting methods to account for differences in pretreatment characteristics (e.g., uterine anatomy—overall uterine size; number, size, and location of individual UF). There are limited comparative data on fertility outcomes among women undergoing myomectomy, and thus, observational studies that are prospective in design can make an important contribution to the literature.

The limitations of the study include the restriction of analyses to women undergoing myomectomy only and the 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 to observe 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 UFs; submucous UFs that could be more strongly associated with inhibition of implantation) (7, 8). Many of the demographic characteristics that are more common among women with severe UFs (e.g., later reproductive age, African ancestry) are also risk factors for adverse reproductive outcomes, such as infertility and spontaneous abortion (58, 59), and could confound the potential association between the 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 UFs who undergo abdominal myomectomy. Whether it is even appropriate to compare abdominal with laparoscopic and hysteroscopic myomectomy is debatable given that a single patient may never be offered all three of these options. However, the extent to which differences in preoperative uterine anatomy or other UF characteristics alone, independent of the route of procedure, would have had a direct effect on the fertility outcomes is unclear. Lack of data on specific types of reproductive failures, such as fertilization, implantation, or postimplantation 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 the differences in fertility success across myomectomy route (60–64).

The COMPARE-UF data were collected from a convenience sample of patients undergoing UF procedures at several clinical sites across the United States; 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 UFs, including subfertility as a syndrome. The proportion of women undergoing hysteroscopic resection reflects the distribution of women with UFs suitable for hysteroscopic resection among our study population, most 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 postprocedure 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. Although reports were abstracted using a standard form that included data on the International Federation of Gynecology and Obstetrics (FIGO) stage, fewer than 2% of COMPARE-UF reports used the FIGO classification. The general categorization of UFs 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 UFs are more likely to contribute to infertility given their ability to cause uterine cavity distortion (11). There is also evidence that the removal of submucous UFs increases subsequent pregnancy rates (11). However, controversy remains about the role of intramural UFs in the pathogenesis of infertility (65). In a recently-published debate (65), experts cited several mechanisms by which intramural UFs 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 favored the removal of intramural UFs to improve fertility. Other experts argued against the removal of intramural UFs to improve fertility, citing concerns about surgical complications and challenges in the interpretation of published studies because of 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 UFs have a limited, if any, impact on fertility although data are also limited, particularly for larger UFs (11). Finally, comparing fertility in women with intramural UFs surrounded by myometrium (FIGO type 4) with those that contact the endometrium (FIGO type 3) is a novel area of investigation (65, 66), but was beyond the scope of this report.

Results from the present study indicated that the probability of pregnancy or live birth during 36 months of follow-up did not differ appreciably according to the surgical route of myomectomy, particularly when comparing abdominal vs. laparoscopic routes, after accounting for pretreatment 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 a change in how the current myomectomy route is chosen by patients in consultation with their providers in regard to a patient's desire for future fertility.

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