Association of uterine fibroids and pregnancy outcomes after ovarian stimulation–intrauterine insemination for unexplained infertility

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Objective: To investigate the association of non–cavity-distorting uterine fibroids and pregnancy outcomes after ovarian stimulation–intrauterine insemination (OS-IUI) in couples with unexplained infertility.
Design: Secondary analysis from a prospective, randomized, multicenter clinical trial investigating fertility outcomes after OS-IUI.
Setting: Reproductive Medicine Network clinical sites.
Patient(s): Nine hundred couples with unexplained infertility who participated in the Assessment of Multiple Intrauterine Gestations from Ovarian Stimulation (AMIGOS) clinical trial.

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Intervention(s): Participants were randomized to one of three arms (clomiphene citrate, letrozole, or gonadotropins), and treatment was continued for up to four cycles or until pregnancy was achieved.
Main Outcomes Measure(s): Conception (serum hCG increase), clinical pregnancy (fetal cardiac activity), and live birth rates.
Result(s): A total of 102/900 participants (11.3%) had at least one documented fibroid and a normal uterine cavity. Women with fibroids were older, more likely to be African American, had a greater uterine volume, lower serum antimüllerian hormone levels, and fewer antral follicles than women without fibroids. In conception cycles, clinical pregnancy rates were significantly lower in participants with fibroids than in those without uterine fibroids. Pregnancy loss before 12 weeks was more likely in African American women with fibroids compared with non-African American women with fibroids. There was no difference in conception and live birth rates in subjects with and without fibroids.
Conclusion(s): No differences were observed in conception and live birth rates in women with non–cavity-distorting fibroids and those without fibroids. These findings provide reassurance that pregnancy success is not impacted in couples with non–cavity-distorting fibroids undergoing OS-IUI for unexplained infertility.
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Key Words: Intrauterine insemination, ovarian stimulation, pregnancy, unexplained infertility, uterine fibroids

Whether uterine fibroids impair pregnancy outcomes has been a longstanding topic of debate (1–7). Increased rates of implantation failure and early pregnancy loss have been consistently reported in women with submucosal fibroids and intramural fibroids that distort the endometrium (8–10). Historically there has been no consensus regarding the association of intramural and/or subserosal fibroids and pregnancy outcomes in women with a normal endometrial cavity contour. In women with intramural fibroids and a normal uterine cavity confirmed by hysteroscopy, saline sonohysterogram, or hysterosalpingogram, some studies have reported no difference in early pregnancy loss (9, 11), ectopic pregnancy (11), and live birth rates (9, 12) compared with women without fibroids and a normal endometrial cavity. In contrast, other studies have reported lower clinical pregnancy and live birth rates in the presence of intramural fibroids without endometrial cavity distortion (1, 4, 13). Because most studies are from a single center with a small sample size, are retrospective, and vary significantly in the selection of control groups and primary endpoints (clinical pregnancy vs. ongoing pregnancy vs. live birth), it is difficult to interpret contradictory results (2,14–19).

In addition to the notion that fibroids cause anatomic disruption and impair fecundity, there is also the thought that both unexplained infertility and fibroids share common underlying mechanisms (6). Specifically, the pathogenesis of unexplained infertility and fibroids may be mediated by inflammatory pathways, hormonal aberrations, and/or genetic alterations, all of which can negatively impact pregnancy outcomes (6, 20). In couples with unexplained infertility, who do not have an identifiable etiology for their inability to conceive, initial empirical treatment commonly involves ovarian stimulation with intrauterine insemination (OS-IUI) (21–23). It is estimated that approximately 10%–50% of reproductive-aged women have uterine fibroids (24, 25), and an estimated 15% of infertile couples have unexplained infertility (6, 26). The Reproductive Medicine Network's (RMN's) Assessment of Multiple Intrauterine Gestations from Ovarian Stimulation (AMIGOS) multicenter, randomized clinical trial provides an opportunity to evaluate the relationship between non–cavity-distorting fibroids and pregnancy outcomes in couples with unexplained infertility (27). The objective of this hypothesis-generating study was to use the AMIGOS database to investigate the association of non–cavity-distorting uterine fibroids and pregnancy outcomes in couples with unexplained infertility undergoing OS-IUI. Because a higher prevalence and greater severity of uterine fibroids has been consistently observed in African American women compared with other racial/ethnic groups (28–31), this study also sought to investigate whether there are race-specific differences in pregnancy outcomes in couples with unexplained infertility and non–cavity-distorting fibroids.

MATERIALS AND METHODS

Study Design

This secondary analysis included all 900 participants from the AMIGOS clinical trial. AMIGOS was a prospective, randomized, multicenter clinical trial that investigated the rate of conception, live birth pregnancy, and multiple gestations associated with OS-IUI in couples with unexplained infertility (27). The trial was conducted at 12 clinical locations in the United States (clinicaltrials.gov number NCT01044862). Randomized treatment arms included clomiphene citrate (300 couples), letrozole (299 couples), and gonadotropin (Menopur, Ferring Pharmaceuticals; 301 couples). Couples underwent OS-IUI treatment in the assigned arm until four cycles were completed or pregnancy occurred. Study participants were women aged ≥ 18 to ≤ 40 years, with regular menses (9 or more per year), a normal uterine cavity, at least one patent fallopian tube, and a male partner with an ejaculated semen specimen of at least 5×10^6 motile sperm. A complete description of study design, inclusion and exclusion criteria, statistical analyses, baseline characteristics, endocrine assays, and treatment outcomes of participants has been previously reported (27, 32, 33). Institutional review board approval was

obtained at each study site, and all participants provided informed consent before participation.

Baseline demographic and reproductive characteristics from all screening ultrasound examinations were recorded for the original study (27, 32). A normal uterine cavity contour and patency of at least one fallopian tube was confirmed with either hysterosalpingogram or sonohysterogram before inclusion in the study (32). Uterine fibroid measurements were recorded in three dimensions with standard 7.5-MHz transvaginal ultrasound examination, and the uterine volume (cubic centimeters [cm^3]) and the volume (cm^3) of the largest fibroid (if present) were recorded for each participant before the first treatment visit during study screening (33). Per the original study design, the total number of fibroids was not recorded.

Data Analyses

Analyses were conducted on 900 AMIGOS patients (combined treatment arms) categorized by the presence or absence of uterine fibroids at the screening visit, with 102 patients with fibroids and 798 without fibroids. Outcomes of this study were conception, clinical pregnancy, pregnancy loss, and live birth. Conception was defined as having an interval increase in serum hCG concentration in consecutive tests; clinical pregnancy was defined as an intrauterine pregnancy with fetal cardiac activity confirmed by transvaginal ultrasound; live birth was defined as the delivery of a viable infant.

Normality was assessed for continuous variables before group comparisons. Most were found to deviate significantly from normality assumption. Hence, summary statistics were presented by interquartile range and median (25th percentile, median, 75th percentile), and the Wilcoxon rank-sum test was used to compare differences between patients with and without fibroids. Categorical variables were presented as number of subjects/total number (percentage), with Fisher's exact test used to test differences between those with and without fibroids. Both unadjusted and adjusted logistic regression analyses were performed to assess the association between pregnancy outcomes and the presence of fibroids. Adjusted logistic regression models of pregnancy outcomes controlled for the variables of treatment type, age, race, ethnicity, body mass index (BMI), endometrial thickness, multiple gestation, IUI semen total motile concentration, prior infertility therapy, uterine volume, serum thyroid peroxidase (TPO) antibody titer, and the presence of serum antichlamydial antibody. The association of race/ethnicity (African American [reference] vs. non-African American [inclusive of white, Asian, Latino, Native American or Alaska Native, mixed race]) and pregnancy outcomes in women with fibroids was evaluated with adjusted logistic regression controlling for the variables of treatment type, age, race, ethnicity, BMI, endometrial thickness, multiple gestation, IUI semen total motile concentration, and prior infertility therapy. Study site as a random effect was not found to significantly impact results and was not included in final multivariable logistic regression models.

Odds ratios, using the group without fibroids as the reference group, and corresponding 95% confidence intervals were presented. Statistical significance was defined as a two-sided P value of $<.05$ without correction for multiple comparisons. All analyses were performed in SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Demographic and reproductive characteristics of the study population are presented in Table 1. In the overall (combined treatment arms) study cohort, 102 participants had fibroids and 798 did not. Within the cohort of participants with fibroids, 91 of 102 (89%) had the volume of the largest fibroid recorded. Study participants with fibroids were older, had a greater BMI and uterine volume, and were more likely to be African American. No differences were observed in prior reproductive history (duration of infertility, prior conception, pregnancy loss, live birth rates, and prior infertility therapy) between groups with and without uterine fibroids. Study participants with fibroids had higher mean serum FSH levels, lower antimüllerian hormone levels, and fewer antral follicles compared with those without. No differences were observed in the presence of serum antichlamydial antibody or serum anti-TPO antibody titers between groups.

Characteristics of ovarian stimulation and IUI in the final treatment cycle are presented in Supplemental Table 1 (available online). No differences were observed in ovarian response (peak serum E_2, number of follicles ≥ 16 mm) or the IUI mean total motile sperm count in treatment cycles of participants with or without fibroids. Endometrial lining thickness on the day of hCG trigger was no different in participants with or without fibroids. No differences were observed in endometrial thickness on the day of hCG trigger among all racial/ethnic groups with fibroids and between African American and non-African American women with and without fibroids (data not shown).

Pregnancy outcomes (unadjusted models) after OS-IUI are presented in Table 2. No differences were observed in overall conception rates between participants with and without fibroids. Among treatment cycles in which conception occurred, lower clinical pregnancy rates were observed in study participants with uterine fibroids compared with those without fibroids (59.5% [22 of 37] vs. 80.1% [237 of 296], $P=.005$). Pregnancy of unknown location was more likely in women with fibroids compared with those without (2 of 37 [5.4%] vs. 1 of 296 [0.3%], $P=.034$). In conception cycles, first-trimester fetal plurality, pregnancy loss, ectopic pregnancy, and live birth rates (total, preterm, and term) were similar in participants with and without fibroids. No differences were observed in live birth outcomes, including gestational age, birth weight, neonatal outcomes, route of delivery, and obstetric complications, in the presence or absence of uterine fibroids (Table 3).

Multivariable models to assess the likelihood of clinical and live birth pregnancy outcomes among subjects with and without fibroids are presented in Table 4. After adjustments for multiple demographic, reproductive, and treatment cycle factors, no differences were observed in conception, clinical pregnancy, pregnancy loss, or live birth outcomes between groups. Further models stratified by race (African

TABLE 1

Demographic and reproductive characteristics.

Characteristic	(+) Fibroids	(−) Fibroids	*P* value
n	102	798	
Age (y)	(32.0, 35.0, 37.0)	(29.0, 32.0, 35.0)	<.001
BMI (kg/m^2)	(23.0, 27.2, 31.2)	(21.9, 25.0, 30.1)	.040
Current smoker	9/102 (8.8)	62/798 (7.8)	.710
Race			<.001
White	62/102 (60.8)	660/798 (82.7)	
Black or African American	27/102 (26.5)	57/798 (7.1)	
Asian	11/102 (10.8)	48/798 (6.0)	
American Indian or Alaska Native	1/102 (1.0)	9/798 (1.1)	
Mixed race	1/102 (1.0)	24/798 (3.0)	
Ethnicity			.420
Hispanic or Latino	13/102 (12.8)	81/798 (10.2)	
Not Hispanic or Latino	89/102 (87.3)	717/798 (89.9)	
Reproductive			
Length of attempting conception (mo)	(18.0, 24.0, 48.0)	(18.0, 24.0, 42.0)	.736
Prior pregnancy	44/102 (43.1)	329/798 (41.2)	.713
Prior pregnancy loss	36/102 (35.3)	238/798 (29.8)	.258
Prior live birth	20/102 (19.6)	163/798 (20.4)	.847
Prior infertility therapy	63/102 (61.8)	436/798 (54.6)	.173
Ovarian reserve testing			
Day 3 ± 1 FSH (U/L)	(5.6, 7.2, 8.9)	(5.6, 6.6, 7.8)	.032
AMH (ng/mL)	(0.8, 1.4, 2.5)	(1.2, 2.2, 3.7)	<.001
Total antral follicles	(11.0, 16.0, 22.0)	(13.0, 18.5, 27.0)	.005
Uterine volume (cm^3)	(115.8, 133.8, 178.0)	(77.5, 104.7, 148.6)	.026
TPO antibody (IU/mL)	(10.0, 11.2, 18.7)	(10.0, 10.6, 18.6)	.896
Chlamydia antibody[a]	8/19 (42.1)	37/164 (22.6)	.088

Note: Combined treatment arms (clomiphene citrate, letrozole, gonadotropins). Data are presented as interquartile range and median (25th percentile, median, 75th percentile) or number of subjects/total number (percentage). Wilcoxon rank-sum test was used for continuous variables and χ^2 or Fisher exact test was used for categorical variables. +/- = presence (+) or absence (-) of uterine fibroids. AMH = antimüllerian hormone.

[a] Test result is from the University of Alabama Chlamydia Research Laboratory, Birmingham, Alabama.

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American [reference] vs. non-African American) to assess the association of uterine fibroids and pregnancy outcomes are presented in Supplemental Table 2. Interaction effect between treatment type and race was not significant (data not shown). African American participants with uterine fibroids were more likely to have a clinical pregnancy loss before 12 weeks' gestation compared with women who were non-African American race with fibroids. No differences were observed in conception, clinical pregnancy, or live birth outcomes among groups.

TABLE 2

Pregnancy outcomes after ovarian stimulation/IUI.

Variable	(+) Fibroids	(−) Fibroids	*P* value
n	102	798	
Conception	37/102 (36.3)	296/798 (37.1)	.872
Clinical pregnancy among cycle with conception	22/37 (59.5)	237/296 (80.1)	.005
Fetal plurality			
Singleton pregnancy	19/37 (51.4)	189/296 (63.9)	.139
Twin pregnancy	2/37 (5.4)	39/296 (13.2)	.285
Triplet pregnancy	1/37 (2.7)	9/296 (3.0)	1.000
Pregnancy loss	15/37 (40.5)	93/296 (31.4)	.264
<12 wk	15/15 (100.0)	80/91 (87.9)	.357
≥12 and <24 wk	0/15 (0.0)	11/91 (12.1)	
Extrauterine pregnancy			
Ectopic	4/37 (10.8)	17/296 (5.7)	.271
Heterotopic	0	0	–
PUL	2/37 (5.4)	1/296 (0.3)	.034
Live birth	21/37 (56.8)	202/296 (68.2)	.161
<37 wk	2/21 (9.5)	39/201 (19.4)	.381
≥37 wk	19/21 (90.5)	162/201 (80.6)	

Note: Combined treatment arms (clomiphene citrate, letrozole, gonadotropins). Data are presented as number of subjects/total number (percentage). The χ^2 or Fisher exact test was used for categorical variables. +/- = presence (+) or absence (-) of uterine fibroids. PUL = pregnancy of unknown location.

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The mean volume (cm^3) ± SD of the largest fibroid was 29.39 ± 76.48 cm^3, and median volume of the largest fibroid was 7.58 cm^3 (interquartile range, 2.29–26.4 cm^3) in participants with fibroids (Supplemental Table 3). The range of fibroid volume was 0.090–504.0 cm^3. There were no significant differences in the mean fibroid volume among racial/ethnic groups or between African American and non-African American women. There was no association between fibroid volume and the likelihood of conception, pregnancy loss, and live birth pregnancy. No differences were observed in the mean uterine volume of African American vs. non-African American women with uterine fibroids (Supplemental Table 3).

DISCUSSION

Although there is a significant proportion of couples with unexplained infertility and a well-known common prevalence of uterine fibroids in reproductive-aged women, it has been unclear whether non–cavity-distorting fibroids contribute to an inability to conceive or negatively impact pregnancy

TABLE 3

Live birth pregnancy outcomes after ovarian stimulation/IUI.

Variable	(+) Fibroids	(−) Fibroids	*P* value
n	21	202	
Gestational age (wk)	(38.0, 39.0, 40.0)	(37.0, 39.0, 39.0)	.083
Birth weight (g)	(2,664.9, 3,203.5, 3,345.2)	(2,636.5, 3,132.6, 3,543.7)	1.000
Birth plurality			
Singleton	18/21 (85.7)	162/202 (80.2)	.772
Twins	2/21 (9.5)	35/202 (17.3)	.540
Triplets	1/21 (4.8)	5/202 (2.5)	.452
Mode of delivery			
Vaginal delivery	10/21 (47.6)	105/197 (53.3)	.620
Cesarean section	11/21 (52.4)	92/197 (46.7)	.620
Instrumented vaginal			
Forceps	0/10 (0.0)	3/105 (2.9)	1.000
Vacuum	2/10 (20.0)	9/105 (8.6)	.244
Obstetric complications			
Gestational diabetes	1/21 (4.8)	21/202 (10.4)	.702
Placenta previa	1/21 (4.8)	10/202 (5.0)	1.000
Preterm labor	2/21 (9.5)	24/202 (11.9)	1.000
Postpartum hemorrhage	1/21 (4.8)	5/202 (2.5)	.452

Note: Combined treatment arms (clomiphene citrate, letrozole, gonadotropins). Data are presented as interquartile range and median (25th percentile, median, 75th percentile) or number of subjects/total number (percentage). Wilcoxon rank-sum test was used for continuous variables and χ^2 or Fisher exact test was used for categorical variables. +/- = presence (+) or absence (-) of uterine fibroids.

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outcomes after conception with OS-IUI. In this secondary analysis of the randomized, multicenter AMIGOS trial, clinical pregnancy rates were significantly reduced in participants with non–cavity-distorting fibroids compared with those without uterine fibroids in conception cycles. However, live birth rates were not different in subjects with fibroids compared with those without. Because many couples may undergo empiric OS-IUI as their initial treatment, the findings of this study provide reassurance that live birth rates are not reduced in women with unexplained infertility, fibroids, and a normal endometrial cavity.

TABLE 4

Association of the presence of uterine fibroids and pregnancy outcome during ovarian stimulation/IUI.

Factor	Presence of fibroids, OR (95% CI)	*P* value
Conception		
Unadjusted	0.97 (0.63–1.48)	.872
Adjusted[a]	0.83 (0.46–1.51)	.546
Clinical pregnancy		
Unadjusted	0.65 (0.40–1.07)	.090
Adjusted[a]	0.88 (0.45–1.70)	.701
Pregnancy loss		
Unadjusted	1.31 (0.73–2.36)	.373
Adjusted[a]	0.50 (0.19–1.30)	.154
Pregnancy loss <12 wk		
Unadjusted	1.55 (0.85–2.81)	.150
Adjusted[a]	0.60 (0.23–1.58)	.302
Live birth		
Unadjusted	0.77 (0.46–1.27)	.299
Adjusted[a]	1.36 (0.71–2.63)	.355
Preterm live birth		
Unadjusted	0.39 (0.09–1.64)	.198
Adjusted[a]	1.09 (0.20–5.94)	.917
Term live birth		
Unadjusted	0.90 (0.53–1.52)	.692
Adjusted[a]	1.41 (0.72–2.77)	.316

Note: Combined treatment arms (clomiphene citrate, letrozole, gonadotropins). CI = confidence interval; OR = odds ratio.

[a] Adjusted for treatment type, age, race, ethnicity, BMI, endometrial thickness, multiple gestation, IUI semen total motile concentration, prior infertility therapy, uterine volume, TPO antibody, Chlamydia antibody.

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There are no prior prospective, randomized studies of this magnitude that evaluate the effect of non–cavity-distorting in couples undergoing OS-IUI with unexplained infertility. Prospective studies investigating the effect of non–cavity-distorting intramural fibroids have mainly been performed with IVF, have been limited in the number of subjects, and have yielded conflicting results. Somewhat similar to our findings, a prospective trial of 434 women undergoing IVF/intracytoplasmic sperm injection demonstrated a significant reduction in clinical and ongoing pregnancy rates and an increase in early pregnancy loss with intramural fibroids ≤5 cm (4). However, live birth rates were not reported, and pregnancy outcomes were not stratified by race/ethnicity. Khalaf et al. (13) compared pregnancy outcomes in women with (n = 122) and without fibroids (control, n = 322) in a prospective comparative study of women undergoing their first three IVF cycles. Over a 12-month period, the investigators reported a 40%–45% reduction in cumulative live birth rates in women with fibroids (13). In another prospective cohort of 61 women with non–cavity-distorting fibroids ≤5 cm undergoing their first IVF cycle, there was no difference in clinical pregnancy or live birth rates compared with age-matched controls without fibroids (23). Although these prospective studies are among the largest reported, they did not consistently adjust for significant confounders, such as age, infertility diagnoses, BMI, reproductive characteristics, anti-TPO antibodies, and anti-chlamydial antibodies. Different primary endpoints (clinical pregnancy, pregnancy loss, ongoing pregnancy, and live birth pregnancy) and inadequate sample sizes lend to

difficulty in interpreting the variable results of prior studies (2,14,15,17–19).

Our finding of increased early pregnancy loss rates in African American women with fibroids has not been reported in prior OS-IUI studies. It is well known that the uterine fibroids in African American women are usually larger, more numerous, and may contribute to a larger uterine volume compared with Caucasian women (24, 30, 34). In agreement with large-scale population studies (35), the prevalence of fibroids in this study was much greater in African American women (27 of 84 [32%]) compared with Caucasian women (62 of 722 [8.6%]). However, there were no significant differences in the mean volume of the largest fibroid among racial/ethnic groups or between African American and non-African American women in our study. Moreover, there was no association between the volume of the largest fibroid and the likelihood of conception, pregnancy loss, and live birth pregnancy. In participants with uterine fibroids, there was no difference in the mean uterine volume between African American and non-African American women with fibroids. A higher rate of early pregnancy loss in African American women (compared with Caucasian women) has been previously reported after IVF (36, 37). However, these studies analyzed pregnancy outcomes from the national assisted reproductive technologies registry, Society of Assisted Reproductive Technologies-Clinic Outcomes Reporting System, which does not specifically record data for fibroids. The significantly increased pregnancy loss rate in African American women with fibroids observed in our study is noteworthy but may be due to type 1 error, should be interpreted with caution, and requires further investigation. It must be noted that the AMIGOS study was designed to evaluate the rate of multiple gestation as the primary endpoint and was not designed to evaluate early pregnancy loss as the primary outcome.

Evidence of reduced ovarian reserve (serum day-3 FSH, antimüllerian hormone, and total antral follicles) in women with uterine fibroids compared with women without fibroids has not been reported previously. Although subjects with fibroids were older, their mean age was still less than 35 years and would not be expected to account for such a significant difference in ovarian reserve testing. It is unknown whether reduced ovarian reserve is related to the presence of fibroids, idiopathic infertility, or both. As mentioned previously, the underlying pathogenesis of unexplained infertility and fibroids may be mediated by aberrant inflammatory pathways and/or gene expression and may negatively impact pregnancy outcomes (e.g., clinical pregnancy in conception cycles in this study) (6). Whether there is a common mediator(s) of fibroids and idiopathic infertility, and whether common pathways impact ovarian reserve, is unclear and requires further study.

The main strength of this secondary analysis is the multicenter design of the primary RMN AMIGOS study. Because it is a large, randomized study to evaluate pregnancy outcomes after OS-IUI in couples with unexplained infertility, the study population was ideal for post hoc analysis of the association of uterine fibroids with pregnancy outcomes. Although the AMIGOS trial was well designed to investigate pregnancy outcomes in couples with unexplained infertility, there are several limitations to consider. The overall prevalence of fibroids was 11% and is less than in prior observational studies for premenopausal women (30, 31). This finding may be due in part to a highly selected unexplained infertility population and/or under-detection of fibroids during study screening. Additionally, this population may have had a small overall fibroid burden, which may have contributed to the null findings of similar live birth rates in subjects with and without fibroids. Notably, the prevalence of fibroids in infertile reproductive-aged women is unknown and may be different than in reproductive-aged fertile women. Although there were race/ethnicity differences in pregnancy loss, the limited number of subjects with fibroids may have impaired the study's power to detect differences in live birth outcomes. In the overall population (Table 2), a lower clinical pregnancy rate (fetal cardiac activity) was observed in patients with fibroids, but no differences were noted in pregnancy loss and live birth rate between groups. This discrepancy may also be due to the limited number of subjects with fibroids and limited power to detect differences in live birth. Because the AMIGOS study comprised an intensively screened population by the RMN, women with a significant fibroid burden would not have been categorized as having unexplained infertility and may have been excluded from the study.

One notable limitation was that AMIGOS did not record the total number of fibroids or the total aggregate volume of all fibroids. According to the available data it was not possible to confirm that African American women in this study had a greater fibroid burden than other groups. Availability of these data would have provided a better means to assess the impact of race-specific non–cavity-distorting fibroid burden on pregnancy outcomes. Additionally, a prior history of myomectomy and/or fibroid recurrence was not recorded in the study. Because African American women are more likely to undergo myomectomy and to have recurrence of fibroids compared with Caucasian women (38, 39), availability of these historical data would have been useful to evaluate the impact of racial differences of fibroid characteristics on outcomes.

In summary, in this prospective clinical trial that evaluated multiple pregnancy rates and pregnancy outcomes associated with OS-IUI for unexplained infertility, the presence of non–cavity-distorting fibroids was not associated with a reduced live birth rate. Although clinical pregnancy rates were reduced in conception cycles of subjects with fibroids, the findings of this study provide reassurance to patients and clinicians that fibroids do not impact live birth outcomes in women with a normal uterine cavity. An increased rate of pregnancy loss in African American women with fibroids raises the question of whether there are race-specific pregnancy outcomes associated with non–cavity-distorting fibroids after conception with OS-IUI and warrant future investigation.

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SUPPLEMENTAL TABLE 1

Treatment cycle characteristics for the last treatment cycle.

Characteristic	(+) Fibroids	(−) Fibroids	*P* value
n	102	798	
Peak E_2 before hCG (pg/mL)	(191.0, 493.0, 924.0)	(167.0, 415.0, 743.0)	.112
Day of hCG trigger	(7.0, 8.0, 10.0)	(8.0, 9.0, 10.0)	.055
Follicles ≥16 mm	(1.0, 2.0, 2.0)	(1.0, 2.0, 3.0)	.887
Endometrial thickness (mm)	(7.0, 9.0, 11.0)	(7.0, 9.0, 11.0)	.462
Total motile semen for IUI ($\times 10^6$/sample)	(27.3, 52.6, 122.0)	(32.4, 70.0, 130.4)	.267

Note: Combined treatment arms (clomiphene citrate, letrozole, gonadotropins). Data are presented as interquartile range and median (25th percentile, median, 75th percentile). Wilcoxon rank-sum test was used for continuous variables. +/- = presence (+) or absence (-) of uterine fibroids.

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SUPPLEMENTAL TABLE 2

Association of pregnancy outcomes and race/ethnicity in the presence of fibroids.

Factor	Non-African American[a] OR (95% CI)	*P* value
Conception		
Unadjusted	0.63 (0.26–1.53)	.305
Adjusted[b]	0.52 (0.17–1.60)	.254
Clinical pregnancy		
Unadjusted	1.82 (0.55–5.95)	.325
Adjusted[b]	3.10 (0.68–14.04)	.142
Pregnancy loss		
Unadjusted	0.24 (0.08–0.76)	.015
Adjusted[b]	0.09 (0.02–0.48)	.005
Pregnancy loss <12 wk		
Unadjusted	0.24 (0.08–0.76)	.015
Adjusted[b]	0.09 (0.02–0.48)	.005
Live birth		
Unadjusted	2.53 (0.68–9.38)	.166
Adjusted[b]	3.10 (0.68–14.04)	.142
Term live birth		
Unadjusted	2.17 (0.58–8.13)	.251
Adjusted[b]	2.32 (0.51–10.52)	.275

Note: Combined treatment arms (clomiphene citrate, letrozole, gonadotropins).
[a] Reference: African American.
[b] Adjusted for treatment type, age, race, ethnicity, BMI, endometrial thickness, multiple gestation, IUI semen total motile concentration, prior infertility therapy.

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SUPPLEMENTAL TABLE 3

Comparison of largest fibroid volume.

Race/ethnicity	N	Mean ± SD (cm^3)	Range	*P* value
White	56	19.81 ± 48.90	0.0140–352.02	.165
Black or African American	24	21.43 ± 20.35	0.090–73.53	
Asian	9	111.89 ± 199.13	1.54–504.0	
American Indian or Alaska Native	1	29.70	–	
Mixed race	1	13.73	–	
Non-African American	67	32.23 ± 88.32	0.0140–504.0	.055
African American	24	21.43 ± 20.35	0.090–73.53	

Note: N = 91 (91 of the 102 patients with fibroids have data for largest fibroid volume). Mean ± SD: 29.39 ± 76.48 cm^3. Median: 7.58 cm^3 (interquartile range, 2.29–26.4). Full range: 0.090–504.0 cm^3.

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