OBSTETRICS

Fibroid tumors are not a risk factor for adverse outcomes in twin pregnancies

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OBJECTIVE: Uterine fibroid tumors have been associated with adverse outcomes in singleton pregnancies. We aimed to estimate risk for adverse obstetric outcomes that are associated with fibroid tumors in twin pregnancies.

STUDY DESIGN: A retrospective cohort study of twin pregnancies with ≥1 fibroid tumor on second trimester ultrasound examination. Outcomes included small-for-gestational-age fetal growth, preterm delivery, preterm rupture of membranes, abruption, preeclampsia, and intrauterine fetal death. Univariable and multivariable analyses were used to evaluate the impact of fibroid tumors on outcomes in twin pregnancies compared with twin pregnancies without fibroid tumors.

RESULTS: Of 2378 nonanomalous twin pregnancies, 2.3% had fibroid tumors. Twin pregnancies with fibroid tumors were no more likely to have small-for-gestational-age growth (40.0% vs 36.0%; adjusted odds ratio, 1.1; 95% confidence interval, 0.7–2.0) or preterm delivery at <34 weeks' gestation (25.0% vs 24.0%; adjusted odds ratio, 1.0; 95% confidence interval, 0.5–1.9) than twin pregnancies without fibroid tumors. Other adverse outcomes were no more likely to occur in twin pregnancies with fibroid tumors than in twin pregnancies without fibroid tumors. Post hoc power calculations suggested >97% power to detect 2-fold differences in small for gestational age and preterm delivery at <34 weeks' gestation.

CONCLUSION: In contrast to data that suggest an increased risk for adverse outcomes in singleton pregnancies with fibroid tumors, twin pregnancies with fibroid tumors do not appear to be at increased risk for complications compared with those pregnancies without fibroid tumors.

Key words: fibroid tumor, preterm birth, twin pregnancy

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Uterine fibroid tumors are the most common benign tumor of the female reproductive tract and occur in 20-50% of reproductive age women. As women age, fibroid tumors become increasingly common, and by menopause the incidence of fibroid tumors may be as high as 70-80%.[1] Fibroid tumors may influence the entire spectrum of reproductive function from alterations in fertility, conception, and implantation events[2,3] to later pregnancy outcomes, such as preterm birth or need for cesarean delivery. Several observational studies have investigated the impact of fibroid tumors on obstetric outcomes in singleton pregnancies with conflicting results. In a cohort of women with singleton pregnancies from our institution, we found a positive association between fibroid tumors and multiple adverse obstetric outcomes that included malpresentation, placenta previa, preterm birth, and intrauterine fetal death.[4]

Given the trend for women to delay childbearing and the high prevalence of fibroid tumors in reproductive age women, the question of whether fibroid tumors influence obstetric outcomes is not infrequent for obstetric providers. In addition, the incidence of twin pregnancies has risen 47% since 1990 and currently accounts for approximately 32 per 1000 births in 2009.[5,6] All previous investigations, which include the one from our institution, estimated the risk for adverse outcomes only among singleton gestations, which left obstetric providers to extrapolate the impact of fibroid tumors in twin pregnancies from singleton studies. Thus, we aimed to investigate whether women with twin pregnancies and fibroid tumors are also at increased risk for adverse obstetric outcomes.

Materials and Methods

This is a retrospective cohort study of all consecutive viable twin gestations who presented for routine second-trimester anatomic ultrasound examination between 1990 and 2007 at Washington University Medical Center. This analysis was performed with the large institutional perinatal database and was approved by the Washington University School of Medicine human studies review board.

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Ultrasound examinations were performed by dedicated obstetric and gynecologic sonographers with final interpretation and diagnoses made by Maternal Fetal Medicine attending physicians. Fetal number, chorionicity, placental location, fetal anatomy, and maternal anatomy are recorded routinely as part of second-trimester anatomic surveys. Gestational age was determined by the best data available from the last menstrual period that was consistent with ultrasound dating (±5 days in the first trimester or ±14 days in the second trimester). If last menstrual period was unknown or inconsistent with ultrasound dating, the pregnancy was dated according to the earliest ultrasound data available. Chorionicity is assigned on the basis of the evaluation of fetal genders, placental masses, visualization of the intersection of fetal membranes with placental masses ("lambda sign"), and thickness of fetal membranes. If chorionicity was determined at an earlier ultrasound examination, repeat examination of the routine markers of chorionicity, as appropriate for gestational age, was performed to confirm that the findings were consistent with previous documentation. Maternal anatomy, which included presence, location, and sizes of the 6 largest or most clinically relevant fibroid tumors were documented according to recommendations of the American Institute of Ultrasound in Medicine.[7] Fibroid size routinely is measured in 3 dimensions. In addition, fibroid location within the uterus and relative to placental location is documented routinely.

Twin pregnancies with ≥1 fibroid tumors were compared with twin pregnancies without fibroid tumors. Obstetric outcomes were collected prospectively as the pregnancies continued through the study period and were entered into the perinatal database by trained obstetric research coordinators. Primary outcomes included preterm delivery and small-for-gestational-age (SGA) infants in 1 or both twins (defined as birthweight <10th percentile for gestational age according to the Alexander growth standard[8]). Other outcomes that were evaluated included placenta previa, placental abruption (defined clinically by the obstetric provider and documented in the medical record), preeclampsia (defined according to criteria established by the American College of Obstetricians and Gynecologists[9]), and intrauterine fetal death at >20 weeks of gestation. Pregnancies that were complicated by major fetal anomalies in either fetus were excluded.

Descriptive statistics were used to calculate the incidence of fibroid tumors in the cohort of twin pregnancies. Baseline maternal characteristics were compared between women with and without fibroid tumors with chi-square or Fisher Exact tests, as appropriate. Univariable analysis was performed for obstetric outcomes of interest to obtain relative risks with 95% confidence intervals. Backward stepwise logistic regression was used to control for pertinent confounding variables. The likelihood ratio test was used to assess the impact of removal of covariates from the model. If there were <10 observations for any cell, multivariable logistic regression was not performed to avoid the potential for misleading estimates of risk. Stratified analysis according to chorionicity and fibroid size was also performed. All outcomes were considered at the level of the pregnancy (not at the level of each individual fetus); therefore, paired analysis was not used. All statistical analyses were performed using STATA software (version 10, Special Edition; StataCorp, College Station, TX).

RESULTS

There were a total of 2445 women with twin pregnancies in the cohort. Of those, 67 women (2.7%) were excluded because of major fetal anomalies, which left 2378 women in the final nonanomalous cohort that was examined for obstetric outcomes. Of 2378 women with nonanomalous twin pregnancies, 55 women (2.3%) had fibroid tumors, and 2323 women (97.7%) did not. Of the 55 pregnancies with fibroid tumors, 51 of the fibroid tumors (92.7%) were <6 cm in greatest dimension, and 4 fibroid tumors (7.3%) were >6 cm.

Women with twin pregnancies that were complicated by fibroid tumors were, on average, more likely to be of advanced maternal age, have gestational diabetes mellitus, report alcohol use, have had a previous cesarean delivery, have lower parity, and have fewer living children compared with women with twin pregnancies without fibroid tumors (Table 1). However, twin pregnancies with fibroid tumors had similar prevalence of black women compared with twin pregnancies without fibroid tumors. In addition, smoking during pregnancy, gestational age at study ultrasound examination, monochorionicity, previous birth of a neonate who weighed <5 pounds, and previous preterm birth did not differ between twin pregnancies with fibroid tumors and twin pregnancies without fibroid tumors.

Pregnancy outcomes are shown in Table 2. Women with twin pregnancies and fibroid tumors were no more likely to deliver preterm at <37 weeks' gestation (71.4% vs 62.3%; adjusted odds ratio [OR], 1.2; 95% confidence interval [CI], 0.7–2.3), <34 weeks' gestation (25.0% vs 24.0%; adjusted OR, 1.0; 95% CI, 0.5–1.9), <28 weeks' gestation (7.1% vs 6.7%; relative risk [RR], 1.0; 95% CI, 0.4–2.9), or <24 weeks' gestation (3.8% vs 3.4%; RR, 1.0; 95% CI, 0.3–4.1) compared with twin pregnancies without fibroid tumors. Similarly, twin pregnancies with and without fibroid tumors had statistically similar risk for preterm premature rupture of membranes (5.7% vs 11.6%; RR, 0.5; 95% CI, 0.2–1.5). There was no difference in risk for placental abruption or preeclampsia in twin pregnancies with or without fibroid tumors. There were no cases of twin pregnancies with placenta previa; therefore, no meaningful comparisons can be made regarding the impact of fibroid tumors on this outcome.

Fetal outcomes are shown in Table 3. There was no increase in the risk for SGA in twin pregnancies in the presence of fibroid tumors relative to twins in the absence of fibroid tumors (40.0% vs 36.0%; adjusted OR, 1.1; 95% CI, 0.7–2.0), even after adjustment for advanced maternal age and alcohol use. In addition, there was no increase in the risk for intrauterine fetal death in twin gestations with fibroid tumors compared with those ges-

tations without (3.6% vs 3.7%; RR, 0.9; 95% CI, 0.2–3.5). However, given the rarity of fetal death, no adjusted analysis could be performed reliably.

Given the known association between chorionicity and pregnancy outcomes, we examined obstetric and fetal outcomes that were associated with fibroid tumors that had been stratified by chorionicity. The results remain the same with no increased risk for adverse outcomes associated with fibroid tumors in either monochorionic or dichorionic twin pregnancies. Obstetric outcomes were then examined and stratified by large (≥6 cm) and small (<6 cm) fibroid size that had been measured in the largest dimension. No differences were observed in the cohort with only small fibroid tumors compared with the cohort with no fibroid tumors. Because there were only 4 cases of fibroid tumors >6 cm, it was difficult to draw meaningful conclusions. However, it is noteworthy that none of the 4 twin pregnancies with large fibroid tumors were complicated by the most severe obstetric outcomes of SGA, intrauterine fetal death, or delivery at <28 weeks.

TABLE 1
Baseline demographic characteristics of twin pregnancies with and without fibroid tumors

Characteristic	Fibroid tumor (n = 55)	No fibroid tumor (n = 2323)	*P* value
Advanced maternal age: >35 y, %	60.0	24.7	< .01
Black race, %	29.1	23.0	.33
Gravidity, n[a]	2.4 ± 1.5	2.6 ± 1.6	.14
Range	2.0–2.8	2.6–2.7	
Parity, n[a]	0.6 ± 1.0	1.0 ± 1.2	< .01
Range	0.4–0.9	1.0–1.1	
Body mass index >30 kg/m^2, %	27.1	20.9	.30
Current smoker, %	7.3	10.6	.4
Alcohol use during pregnancy, %	21.8	12.3	.03
Current diagnosis of gestational diabetes mellitus, %	17.6	6.1	< .01
Preexisting diabetes mellitus, %	1.8	1.2	.65
Current diagnosis of chronic hypertension, %	5.5	2.8	.28
Gestational age at study ultrasound examination, wk[a]	19.8 ± 1.7	19.7 ± 1.6	.6
Range	19.3–20.2	19.6–19.8	
Monochorionic gestation, %	19.6	23.0	.56
Previous preterm birth, %	1.8	6.6	.14
Spontaneous abortions, n[a]	0.3 ± 0.6	0.4 ± 0.7	.58
Range	0.2–0.5	0.3–0.4	
Living children, n[a]	0.6 ± 1.0	1.0 ± 1.2	.03
Range	0.4–0.9	0.9–1.0	
Previous cesarean delivery, %	1.8	1.4	< .01
Previous birth of neonate weighing <5 lbs, %	7.3	7.3	.98

[a] Data are given as mean ± SD.

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COMMENT

This cohort of twin pregnancies suggests that those pregnancies with fibroid tumors do not have significantly increased risk for adverse obstetric outcomes compared with twin pregnancies without fibroid tumors. Specifically, we found no increased risk for preterm birth, preterm premature rupture of membranes, placental abruption, SGA, or intrauterine fetal death when we compared them with twin pregnancies without fibroid tumors.

Multiple studies have investigated the impact of fibroid tumors on pregnancy outcomes in singleton gestations.[10-16] However, no previous studies have commented on the impact of fibroid tumors in twin pregnancies, which left providers to extrapolate associations from studies of singletons. A retrospective cohort of >64,000 singleton pregnancies from our institution found an increased risk for placenta previa, placental abruption, preterm birth, and intrauterine fetal death in women with fibroid tumors compared with those women without fibroid tumors.[4] In a retrospective cohort study of >100,000 patients, Sheiner et al[12] reported an increased risk for abruption and preterm labor in singleton pregnancies with fibroid tumors. Qidwai et al[14] evaluated a cohort of 15,000 pregnancies that underwent second-trimester ultrasound examination and found an increased risk for preterm delivery and placenta previa that was associated with fibroid tumors, but no increased risk for preterm rupture of membranes or abruption. However, both studies included only singleton pregnancies. Exclusion of multiple gestations in these studies was appropriate because the increased risk for complications that are associated with multiple gestations would likely confound the interpretation of complications that were associated specifically with fibroid tumors in cohorts that were primarily singletons. However, given mounting data that fibroid tumors are associated with increased obstetric risk in singleton pregnancies, the question remained whether twin pregnancies with fibroid tumors were also at increased risk for complications.

Given the negative findings of this study, one interpretation is that the out-

TABLE 2
Pregnancy-related adverse outcomes for twin pregnancies with (n = 55) and without (n = 2323) fibroids

Outcome	Fibroid tumor, %	No fibroid tumor, %	Unadjusted relative risk (95% CI)	Adjusted odds ratio (95% CI)	*P* value
Delivery at <37 wk gestation	71.4	62.3	1.1 (1.0–1.4)	1.2 (0.7–2.3)[a]	.17
Delivery at <34 wk gestation	25.0	24.0	1.0 (0.7–1.6)	1.0 (0.5–1.9)[b]	.80
Delivery at <28 wk gestation	7.1	6.7	1.0 (0.4–2.7)	NA	.9
Delivery at <24 wk gestation	3.8	3.4	1.0 (0.3–4.1)	NA	.9
Preterm premature rupture of membranes	5.7	11.6	0.5 (0.2–1.5)	NA	.2
Placenta previa	0	0.8	NA	NA	.52
Abruption	1.9	1.9	1.0 (0.1–7.3)	NA	.98
Preeclampsia	19.2	20.0	1.0 (0.5–1.7)	0.9 (0.4–1.9)[c]	.69

CI, confidence interval; *NA*, not applicable.

[a] Adjusted for advanced maternal age, tobacco use, previous preterm birth; [b] Adjusted for previous preterm birth; [c] Adjusted for parity, body mass index.

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comes are rare, and, with the fixed number of patients in the cohort, we were not powered to detect a significant difference. However, a post hoc power calculation was performed that revealed that we had >99% and >97% power to detect a 2-fold increased risk for SGA and preterm birth at <34 weeks gestation, respectively. Thus, we argue that the negative findings in this study are not attributable to a type 2 error. Instead, a more probable explanation is that twin pregnancies are surveyed more frequently with growth ultrasound examinations and antenatal testing; thus, the risks for adverse outcomes that are seen in singleton cohorts with fibroid tumors may be avoided in twin gestations. At our institution, twins generally are treated with ultrasound examination for fetal growth every 2-4 weeks. Antenatal testing with nonstress tests or biophysical profiles are used in twin pregnancies at 32-34 weeks gestation or earlier if an indication arises (for example preeclampsia or twin-twin transfusion syndrome).[17] Thus, we propose that one interpretation of our findings may be that testing routinely, when applied to fetal well-being in twins and planned earlier deliveries in twins, may be mitigating adverse effects that could be attributable to fibroid tumors that are detected in singleton cohorts. The singleton cohort from our institution demonstrated a slightly increased risk for preterm birth that was associated with fibroid tumors in contrast to no increased risk for preterm birth that was demonstrated in this cohort of twins.[4] We propose that the multiple risk factors that increase the risk for preterm birth in twins, relative to singletons generally (eg, uterine distension, indicated preterm delivery), likely blunt the mild effect of fibroid tumors on the risk for preterm birth that is demonstrated in the singleton cohort.

Our study has several limitations. First, although this was a large cohort of twin pregnancies that were available for investigation, the number of twin pregnancies with fibroid tumors was small enough that further stratification by fibroid size would yield unstable results with wide confidence intervals and therefore was not performed. Second, the location of the fibroid tumor within the uterine wall was not known. However, we previously demonstrated that the location of fibroid tumors with respect to the placenta does not matter and that pregnancies with a directly subplacental fibroid tumor have similar risks as pregnancies with a fibroid tumor distant from the placenta.[4] Third, ascertainment of fibroid tumors based on ultrasound examination during pregnancy may be imperfect. We propose that ultrasound examination is the most clinically relevant tool. Furthermore, the most likely direction for ascertainment bias in an ultrasound diagnosis is misclassification of patients with fibroid tumors as control subjects or missing a fibroid that is present. This misclassification would bias

TABLE 3
Fetal adverse outcomes for twin pregnancies with and without fibroids

Outcome	Fibroid tumor, %	No fibroid tumor, %	Unadjusted relative risk (95% CI)	Adjusted odds ratio (95% CI)	*P* value
Intrauterine growth restriction	40.0	36.0	1.1 (0.8–1.5)	1.1 (0.7–2.0)[a]	.6
Intrauterine fetal death	3.6	3.7	0.9 (0.2–3.5)	NA	.9

NA, not applicable.

[a] Adjusted for advanced maternal age and alcohol use.

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our results toward the null. Last, this study included pregnancies at >20 weeks of gestation; therefore, no conclusions regarding the impact of fibroid tumors earlier in pregnancy can be made.

Generalizability of this observational cohort should be considered because this population represents the wide spectrum of patients that is typical of an urban tertiary care referral center. Strengths of our study include the large cohort size of twin pregnancies that facilitated comparisons with adequate power and the ability to perform adjusted analysis for some outcomes. Furthermore, this is the first investigation on the impact of fibroid tumors specifically in twin pregnancies.

In summary, this investigation suggests that twin pregnancies with fibroid tumors are not at increased risk for adverse obstetric outcomes beyond that which exists for twin gestations without fibroid tumors. Specifically, adverse outcomes that previously were demonstrated in cohorts of singleton pregnancies with fibroid tumors are not seen in this cohort of twin pregnancies with fibroid tumors. Screening strategies that are already in place for women with twin pregnancies do not need to be altered based on the presence or absence of fibroid tumors. ■

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