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Fibroids Are Not A Risk Factor For Adverse Outcomes in Twin Pregnancies

Molly J. STOUT, MD¹, Anthony O. ODIBO, MD, MSCE¹, Anthony L. SHANKS, MD¹, Ryan E. LONGMAN, MD¹, George A. MACONES, MD, MSCE¹, and Alison G. CAHILL, MD, MSCI¹

¹Washington University in Saint Louis, Department of Obstetrics and Gynecology

Abstract

Objective—Uterine fibroids have been associated with adverse outcomes in singleton pregnancies. We aimed to estimate risk for adverse obstetric outcomes associated with fibroids in twin pregnancies.

Study Design—A retrospective cohort study of twin pregnancies with 1 fibroid on second trimester ultrasound. Outcomes included small for gestational age (SGA) 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 fibroids on outcomes in twin pregnancies compared to twin pregnancies without fibroids.

Results—Of 2,378 nonanomalous twin pregnancies, 2.3% had fibroids. Twin pregnancies with fibroids were no more likely to have SGA growth (40.0% vs. 36.0%, aOR 1.1, 95%CI 0.7-2.0) or preterm delivery < 34 weeks (25.0% vs. 24.0%, aOR 1.0, 95%CI 0.5-1.9) than twin pregnancies without fibroids. Other adverse outcomes were no more likely to occur in twin pregnancies with fibroids than twin pregnancies without fibroids. Post hoc power calculations suggested greater than 97% power to detect 2-fold differences in small for gestational age and preterm delivery <34 weeks.

Conclusions—In contrast to data suggesting an increased risk for adverse outcomes in singleton pregnancies with fibroids, twin pregnancies with fibroids do not appear to be at increased risk for complications compared to those without fibroids.

Keywords

Fibroids; twin pregnancies; preterm birth

Introduction

Uterine fibroids are the most common benign tumor of the female reproductive tract and occur in 20-50% of reproductive age women. As women age, fibroids become increasingly

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Corresponding Author: Molly J. Stout, MD 660 S. Euclid Ave. Box 8064 Saint Louis, MO 63110 Phone: 314-362-7300 Fax: 314-747-1720 stoutm@wudosis.wustl.edu.

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common and by menopause the incidence of fibroids may be as high as 70-80%¹. Fibroids 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 section. Several observational studies have investigated the impact of fibroids 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 fibroids and multiple adverse obstetric outcomes including malpresentation, placenta previa, preterm birth, and intrauterine fetal death⁴.

Given the trend for women to delay childbearing, and the high prevalence of fibroids in reproductive age women, the question of whether fibroids 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, including the one from our institution, estimated risk for adverse outcomes only among singleton gestations, leaving obstetric providers to extrapolate the impact of fibroids in twin pregnancies from singleton studies. Thus, we aimed to investigate whether women with twin pregnancies and fibroids 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 using the large institutional perinatal database and was approved by the Washington University School of Medicine human studies review board.

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 routinely recorded as part of second trimester anatomic surveys. Gestational age was determined by the best data available from the last menstrual period (LMP) consistent with ultrasound dating (± 5 days in the first trimester or ± 14 days in the second trimester). If LMP was unknown or inconsistent with ultrasound dating, the patient was dated according to the earliest ultrasound available. Chorionicity is assigned based on 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, including presence, location, and sizes of the 6 largest or most clinically relevant fibroids were documented according to recommendations of the American Institute of Ultrasound in Medicine recommendations⁷. Fibroid size is routinely measured in three dimensions. In addition, fibroid location within the uterus and relative to placental location is routinely documented.

Women with twin pregnancies and one or more fibroids were compared to twin pregnancies without fibroids. Obstetric outcomes were collected prospectively as pregnancies continued through the study period and entered into the perinatal database by trained obstetric research coordinators. Primary outcomes included preterm delivery and SGA in one or both twins (defined as birth weight less than the 10th percentile for gestational age according to the Alexander growth standard⁸). Other outcomes 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 Gynecologists⁹), and intrauterine fetal death after 20 weeks of gestation. Pregnancies complicated by major fetal anomalies in either fetus were excluded.

Descriptive statistics were used to calculate the incidence of fibroids in the cohort of twin pregnancies. Baseline maternal characteristics were compared between women with and without fibroids using 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 fewer than 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) and thus paired analysis was not used. All statistical analyses were performed using *STATA V10, Special Edition* (College Station, TX, USA www.stata.com).

Results

There were a total of 2445 women with twin pregnancies in the cohort. Of those, 2.7% (n=67) were excluded for major fetal anomalies, leaving 2378 in the final non-anomalous cohort examined for obstetric outcomes. Of 2378 women with non-anomalous twin pregnancies, 2.3% (n=55) had fibroids and 97.7% (n=2323) did not. Of the 55 pregnancies with fibroids 51 (92.7%) of the fibroids were less than 6cm in greatest dimension and 4 (7.3%) were greater than 6cm.

Women with twin pregnancies complicated by fibroids were, on average, more likely to be of advanced maternal age, have gestational diabetes, report alcohol use, have had a prior cesarean section, have lower parity, and have fewer living children compared to women with twin pregnancies without fibroids (Table 1). However, twin pregnancies with fibroids had similar prevalence of Black women compared to twin pregnancies without fibroids. In addition, smoking during pregnancy, gestational age at study ultrasound, monochorionicity, previous birth of a neonate weighing less than 5 pounds, and prior preterm birth did not differ between twin pregnancies with fibroids compared to twin pregnancies without fibroids.

Pregnancy outcomes are shown in Table 2. Women with twin pregnancies and fibroids were no more likely to deliver preterm at less than 37 (71.4% vs. 62.3%, aOR 1.2, 95%CI 0.7-2.3), less than 34 (25.0% vs. 24.0%, aOR 1.0, 95%CI 0.5-1.9), less than 28 (7.1% vs. 6.7%, RR 1.0 95%CI 0.4-2.9), or less than 24 weeks (3.8% vs. 3.4%, RR 1.0, 95% 0.3-4.1) compared to twin pregnancies without fibroids. Similarly, twin pregnancies with and without fibroids 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 fibroids. There were no cases of twin pregnancies with placenta previa and therefore no meaningful comparisons can be made regarding the impact of fibroids 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 fibroids relative to twins in the absence of fibroids (40.0% vs. 36.0%, aOR 1.1 95%CI 0.7-2.0) even after adjusting for advanced maternal age and alcohol use. In addition, there was no increase in the risk for intrauterine fetal death in twin gestations with fibroids compared to those 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 reliably performed.

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

Comment

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

Multiple studies have investigated the impact of fibroids on pregnancy outcomes in singleton gestations¹⁰⁻¹⁶. However, no prior studies have commented on the impact of fibroids in twin pregnancies, leaving providers to extrapolate associations from studies of singletons. A retrospective cohort of more than 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 fibroids compared to those without fibroids⁴. In a retrospective cohort study of more than 100,000 patients Sheiner et al reported an increased risk for abruption and preterm labor in singleton pregnancies with fibroids¹². Qidwai et al evaluated a cohort of 15,000 pregnancies that underwent second trimester ultrasound and found an increased risk for preterm delivery and placenta previa associated with fibroids, but no increased risk for preterm rupture of membranes or abruption. However, both studies only included singleton pregnancies¹⁴. Exclusion of multiple gestations in these studies was appropriate, as the increased risk for complications associated with multiple gestations would likely confound the interpretation of complications specifically associated with fibroids in cohorts that are primarily singletons. However, given mounting data that fibroids are associated with increased obstetric risk in singleton pregnancies, the question remained whether twin pregnancies with fibroids were also at increased risk for complications.

Given the negative findings of this study, one interpretation is that the outcomes are rare and 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 which revealed that we had greater than 99% and 97% power to detect a two-fold increased risk for SGA and preterm birth less than 34 weeks 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 ultrasounds and antenatal testing and thus, the risks for adverse outcomes seen in singleton cohorts with fibroids may be avoided in twin gestations. At our institution twins are generally managed with ultrasound for fetal growth every 2-4 weeks. Antenatal testing with nonstress tests or biophysical profiles are used in twin pregnancies at 32-34 weeks or earlier if an indication arises (for example pre-eclampsia or twin-twin transfusion syndrome)¹⁷. Thus, we propose that one interpretation of our findings may be that testing routinely applied fetal well-being in twins and planned earlier deliveries in twins may be mitigating adverse effects attributable to fibroids detected in singleton cohorts. The singleton cohort from our institution demonstrated a slightly increased risk for preterm birth associated with fibroids in

contrast to no increased risk for preterm birth demonstrated in this cohort of twins⁴. We propose that the multiple risk factors which increase the risk for preterm birth in twins relative to singletons generally (uterine distension, indicated preterm delivery etc.) likely blunt the mild effect of fibroids on the risk for preterm birth demonstrated in the singleton cohort.

Our study has several limitations. Although this is a large cohort of twin pregnancies available for investigation, the number of twin pregnancies with fibroids was small enough that further stratification by fibroid size would yield unstable results with wide confidence intervals and thus was not performed. Second, the location of the fibroid within the uterine wall is not known. However we previously demonstrated that location of fibroids with respect to the placenta does not matter and pregnancies with a directly sub-placental fibroid have similar risk as pregnancies with a fibroid distant from the placenta⁴. Third, ascertainment of fibroids based on ultrasound during pregnancy may be imperfect. However, we propose that ultrasound is the most clinically relevant tool. Furthermore, the most likely direction for ascertainment bias in ultrasound diagnosis is misclassification of patients with fibroids as controls, or missing a fibroid that is present. This misclassification would bias our results toward the null. Lastly this study included pregnancies beyond 20 weeks of gestation and thus no conclusions regarding the impact of fibroids earlier in pregnancy can be made.

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

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

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Condensation

Women with twin pregnancies and fibroids are not at increased risk for adverse obstetric outcomes compared to twin pregnancies without fibroids.

Table 1

Baseline demographic and medical characteristics of twin pregnancies with fibroids compared to twin pregnancies without fibroids.

Characteristic	Fibroid (n=55)	No Fibroid (n=2323)	p-value
Advanced maternal age (>35 years old)(%)	60.0	24.7	<0.01
Black race (%)	29.1	23.0	0.33
Gravidity (mean±SD)	2.4 ± 1.5 (2.0-2.8)	2.6 ± 1.6 (2.6-2.7)	0.14
Parity (mean±SD)	0.6 ± 1.0 (0.4-0.9)	1.0 ± 1.2 (1.0-1.1)	<0.01
Body Mass Index > 30 (%)	27.1	20.9	0.30
Current smoker (%)	7.3	10.6	0.4
Alcohol use during pregnancy (%)	21.8	12.3	0.03
Current diagnosis of gestational diabetes (%)	17.6	6.1	<0.01
Preexisting diabetes mellitus (%)	1.8	1.2	0.65
Current diagnosis of chronic hypertension (%)	5.5	2.8	0.28
Gestational age at study ultrasound (weeks ± SD)	19.8 ± 1.7 (19.3-20.2)	19.7 ± 1.6 (19.6-19.8)	0.6
Monochorionic Gestation (%)	19.6	23.0	0.56
Prior preterm birth (%)	1.8	6.6	0.14
Number of spontaneous abortions (mean±SD)	0.3 ± 0.6 (0.2-0.5)	0.4 ± 0.7 (0.3-0.4)	0.58
Number of living children (mean±SD)	0.6 ± 1.0 (0.4-0.9)	1.0 ± 1.2 (0.9-1.0)	0.03
Previous cesarean section (%)	1.8	1.4	<0.01
Previous birth of neonate weighing less than 5 pounds (%)	7.3	7.3	0.98

Table 2
Pregnancy-level adverse outcomes for twin pregnancies with fibroids compared to no fibroids.

Outcome	Fibroid (n=55)	No Fibroid (n=2323)	Unadjusted Relative Risk (95% CI)	Adjusted Odds Ratio (95% CI)	p-value
Delivery less than 37 weeks	71.4%	62.3%	1.1 (1.0-1.4)	1.2 ^a (0.7-2.3)	0.17
Delivery less than 34 weeks	25.0%	24.0%	1.0 (0.7-1.6)	1.0 ^b (0.5-1.9)	0.80
Delivery less than 28 weeks	7.1%	6.7%	1.0 (0.4-2.7)	NA	0.9
Delivery less than 24 weeks	3.8%	3.4%	1.0 (0.3-4.1)	NA	0.9
Preterm premature rupture of membranes	5.7%	11.6%	0.5 (0.2-1.5)	NA	0.2
Placenta previa	0	0.8	NA	NA	0.52
Abruption	1.9%	1.9%	1.0 (0.1-7.3)	NA	0.98
Pre-eclampsia	19.2%	20.0%	1.0 (0.5-1.7)	0.9 ^c (0.4-1.9)	0.69

^a Adjusted for advanced maternal age, tobacco use, prior preterm birth

^b Adjusted for prior preterm birth

^c Adjusted for parity, body mass index

Table 3

Fetal adverse obstetric outcomes for twin pregnancies with fibroids compared to no fibroids.

Outcome	Fibroid	No Fibroid	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 ^a (0.7-2.0)	0.6
Intrauterine fetal death	3.6%	3.7%	0.9 (0.2-3.5)	NA	0.9

^a Adjusted for advanced maternal age and alcohol use