Leiomyomatous uterus and preterm birth: an exposed/unexposed monocentric cohort study

Aude Girault, MD; Camille Le Ray, MD, PhD; Charles Chapron, MD, PhD; François Goffinet, MD, PhD; Louis Marcellin, MD, PhD

BACKGROUND: The risk of preterm birth may increase in the presence of uterine leiomyomas during pregnancy. Whether myomectomy abrogates this risk has never been studied.

OBJECTIVE: Our aim was to evaluate the association between the presence of uterine leiomyomas during pregnancy and preterm birth and, if an association exists, to evaluate its persistence in case of a history of myomectomy.

STUDY DESIGN: This exposed/unexposed monocentric retrospective cohort study included all women with singleton pregnancies delivering >22 weeks in a tertiary university hospital maternity unit from January 2011 through September 2015. Women with a leiomyomatous uterus were compared to women with no myomas. Women in the leiomyomatous uterus group were women with uterine leiomyoma(s) during pregnancy (≥1 leiomyoma, measuring ≥20 mm or multiple leiomyomas whatever the size) seen on at least 1 obstetric ultrasound without history of myomectomy, or women with a history of myomectomy (removal of ≥1 leiomyoma, measuring ≥20 mm or multiple leiomyomas whatever the size) by hysteroscopy, laparoscopy, or laparotomy with or without persistent leiomyomas. The association between leiomyomatous uterus and preterm birth was assessed through univariate and multivariable logistic regression.

RESULTS: Among the 19,866 women in the cohort, 301 (1.5%) had a leiomyomatous uterus (154 unoperated women and 147 operated women). The rate of premature delivery was 12.0% in the leiomyomatous uterus group and 8.4% in the nonleiomyomatous uterus group. After adjusting for the risk factors for preterm birth, leiomyomatous uterus was significantly associated with preterm birth (adjusted odds ratio, 2.5; 95% confidence interval, 1.7—3.7). This association was significant for unoperated women (adjusted odds ratio, 2.7; 95% confidence interval, 1.6—4.6) as well as operated women (adjusted odds ratio, 2.3; 95% confidence interval, 1.3—3.9) when compared to the nonleiomyomatous uterus group.

CONCLUSION: Uterine leiomyomas are associated with preterm birth and this association persists after myomectomy.

Key words: leiomyomas, myomectomy, pregnancy outcomes, premature obstetric labor, preterm birth

Introduction

Uterine leiomyoma is the most frequent benign uterine tumor affecting 1—10% of reproductive-aged women.[1—3] The prevalence of leiomyomas in pregnant women varies between 0.4% and 10.7%.[1—4] Several observational studies evaluating the effect of leiomyomas on pregnancy outcomes have been published.[1,2,4—11] They report conflicting results concerning the association between leiomyomas and preterm birth, hospitalization for threatened preterm birth, preterm premature rupture of the membrane (PPROM), intrauterine growth retardation (IUGR), preeclampsia, and cesarean delivery.[1,2,4—11] Focusing on prematurity, when an association is described it is unclear whether it concerns spontaneous or induced preterm birth. In addition to the heterogeneity of the results, these studies are limited by the low number of included cases and by the classification bias due to the methods employed to diagnose the leiomyomas.[8,9]

How uterine leiomyomas could negatively impact pregnancy course remains unclear. Moreover, the study of the association between history of myomectomy and unfavorable pregnancy outcomes is lacking. Myometrium is an important reproductive tissue that controls the pregnancy maintenance as well as the onset of labor using a complex biomolecular system coordinated by endocrine, paracrine, and immunoregulatory factors.[11—13] The junction area between the endometrium and the myometrium seems to be the site of physicochemical and vascular phenomena disturbed in the case of uterine leiomyoma.[14,15] Therefore, presence of uterine leiomyomas or history of myomectomy may impair the uteroplacental interface and increase both the risk of spontaneous preterm birth and induced preterm birth due to vascular pathologies (preeclampsia, gestational hypertension, IUGR).

Thus, our original hypothesis was that there is an association between presence of leiomyoma during pregnancy and preterm birth, and that this association is persistent after myomectomy.

We therefore decided to carry out a large cohort study to evaluate the association between the presence of uterine leiomyomas and preterm birth <37 weeks and to evaluate, if this association exists, its persistence in case of history of myomectomy.

Materials and Methods

We performed a retrospective cohort study using hospital data from Jan. 1, 2011, through Sept. 31, 2015, in a tertiary university hospital maternity unit (Port Royal Maternity, Cochin Hospital, Paris, France). All women with a singleton fetus delivered in the maternity unit >22^{+0} weeks during the study period were included. Women referred from other hospitals during their pregnancy were excluded. This study was approved by the National Data Protection Authority (Commission Nationale de l'Informatique et des Libertés no. 1755849). Under French regulations,

Cite this article as: Girault A, Le Ray C, Chapron C, et al. Leiomyomatous uterus and preterm birth: an exposed/unexposed monocentric cohort study. Am J Obstet Gynecol 2018;219:410.e1-7.

0002-9378/$36.00

https://doi.org/10.1016/j.ajog.2018.08.033

AJOG at a Glance

Why was this study conducted?

To evaluate the association between the presence of uterine leiomyomas during pregnancy and preterm birth and, if an association exists, to evaluate its persistence in case of myomectomy.

Key findings

The rate of premature birth was higher in both women with leiomyomas during pregnancy and women with a history of myomectomy compared to women with a nonleiomyomatous uterus. After adjusting for the risk factors for preterm birth, leiomyomatous uterus was significantly associated with preterm birth. This association was significant for both unoperated and operated women when compared to the nonleiomyomatous uterus group.

What does this add to what is known?

This cohort study shows that women with a leiomyomatous uterus are at risk of preterm birth and that this risk persists after myomectomy.

this study is exempt from institutional review board review because it is an observational study using anonymized data from medical records. Women are informed that their records can be used for the evaluation of medical practices and are allowed to opt out of these studies. The study's exempt status was confirmed by the Institutional Review Board Ile-de-France.

All women had a first-trimester ultrasound and gestational age was confirmed by ultrasound measurement of the craniocaudal length between 11^{+0} and 13^{+6} weeks of gestation. If the pregnancy resulted from assisted reproductive therapy (ART), gestational age was determined from the date of in vitro fertilization. As recommended in France, at least 3 prenatal ultrasounds were performed during pregnancy, 1 at each trimester. It has to be noted that there is no recommendation regarding the screening of leiomyomas in France.[16]

The cohort of women was separated into 2 groups named "leiomyomatous uterus" and "nonleiomyomatous uterus" depending on the exposure to leiomyomas. Leiomyomatous uterus was defined by the presence of uterine leiomyoma(s) during pregnancy ($\geq$1 leiomyoma, measuring $\geq$20 mm or multiple leiomyomas whatever the size) seen on at least 1 obstetric ultrasound without history of myomectomy, or as a history of myomectomy (removal of $\geq$1 leiomyoma, measuring $\geq$20 mm or multiple leiomyomas whatever the size) by hysteroscopy, laparoscopy, or laparotomy with or without persistent leiomyomas. Then, the group of leiomyomatous uterus was categorized into unoperated and operated leiomyomatous uterus depending on the history of myomectomy.

The primary outcome was preterm birth <37 weeks whatever the cause. The secondary outcomes were spontaneous preterm birth, defined as a delivery <37 weeks either spontaneous or induced after PPROM or chorioamnionitis; and induced preterm birth, defined as a delivery <37 weeks after induction of labor or cesarean delivery before labor, for uncontrolled gestational hypertension, preeclampsia, IUGR, placenta abruption, or hemorrhage following placenta previa.

Data were collected retrospectively using the women's electronic medical files. Women with a leiomyomatous uterus were identified in the obstetrical electronic medical database by a multiple combination of key words. For women with leiomyomatous uterus, all the manuscript medical files were reviewed to obtain detailed information on the number, size, and localization of the leiomyomas on the ultrasounds and surgical reports.

We collected all the characteristics potentially related to preterm birth. This included women's preexisting characteristics (age; geographical origin; body mass index [BMI]; medical history, eg, diabetes and high blood pressure; parity; history of cesarean; history of premature delivery; use of ART) and pregnancy characteristics (gestational hypertension, gestational diabetes, other significant medical pathology). We also collected the pregnancy-related complications (PPROM, preeclampsia, placenta previa, gestational age at rupture of the membranes, hospitalization during pregnancy) and the pregnancy outcomes (onset of labor, gestational age at delivery, fetal presentation, type and mode of delivery, postpartum hemorrhage and transfusion).

Our variable of interest, leiomyomatous uterus, was used first as a binary variable (leiomyomatous uterus and nonleiomyomatous uterus), then as a 3-category variable coded as follow: nonleiomyomatous uterus, unoperated leiomyomatous uterus, and operated leiomyomatous uterus.

The analysis started by a comparison of the general characteristics, the pregnancy characteristics, the delivery characteristics, and the pregnancy outcomes of the population between the leiomyomatous uterus group and the nonleiomyomatous uterus group. We performed Pearson χ^2 tests to compare qualitative variables and Student *t* test to compare quantitative variables between the 2 groups.

To identify the variables associated with preterm birth, we first performed a univariate analysis comparing the association between preterm birth and women's preexisting and pregnancy characteristics. We then created 2 multivariable models; one included the binary variable leiomyomatous uterus and the other included the 3-category variable (nonleiomyomatous uterus, unoperated leiomyomatous uterus, or operated leiomyomatous uterus). The adjusted odds ratios (aOR) and their 95% confidence intervals (CI) reflecting the association between our variable of interest, leiomyomatous uterus, and the primary outcome, premature delivery, were assessed through these multivariable logistic regression models. The multivariable models included the characteristics known in literature as