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Amrin Khander, Erica Stern, Rachel S. Gerber & Nathan S. Fox

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ORIGINAL ARTICLE

The association between obstetrical history and preterm birth in women with uterine anomalies

Amrin Khander[a], Erica Stern[a], Rachel S. Gerber[b] and Nathan S. Fox[a,c]

[a]Department of Obstetrics, Gynecology and Reproductive Science, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [b]Department of Obstetrics and Gynecology, New York Presbyterian – Weill Cornell Medical College, New York, NY, USA; [c]Maternal Fetal Medicine Associates, PLLC, New York, NY, USA

ABSTRACT

Objective: To estimate the association between obstetric history and preterm birth in women with uterine anomalies.

Methods: This was a retrospective cohort study of women with uterine anomalies managed by one maternal–fetal medicine practice from 2005 to 2016. Women were separated into three groups based on their most recent pregnancy outcome: preterm birth <37 weeks, nulliparous, and term birth. Delivery outcomes were compared across the three groups, with the primary outcome being preterm birth <37 weeks. A subgroup analysis was performed in women with major uterine anomalies (unicornuate, bicornuate, and didelphys).

Results: A total of 283 women with uterine anomalies were included. Preterm birth <37 weeks was 60.4% in women with prior preterm birth versus 18.2% in nulliparous women, versus 15.8% in women with a prior term birth ($p < .001$). The difference between nulliparous women and women with a prior term birth was not significant ($p = .635$). Among the 118 women with major uterine anomalies, the likelihood of preterm birth was also highest in the prior preterm birth group (71.4 versus 26.1 versus 25.0%, $p < .001$), and the difference between nulliparous women and women with a prior term birth was not significant ($p = .906$).

Conclusions: In women with uterine abnormalities, a prior preterm birth is significantly associated with recurrent preterm birth. However, a prior term birth does not lower the risk of preterm birth as compared to nulliparous women.

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Introduction

Congenital uterine anomalies, also known as mullerian anomalies, are a result of abnormal fusion and embryologic development of the mullerian ducts leading to abnormal uterine cavities. They are present in approximately 2–4% of the overall population [1–4] and are more common in women with poor reproductive histories [4,5]. Uterine anomalies include several abnormalities, ranging from milder defects such as an arcuate uterus to more severe defects, such as complete failure of fusion (uterine didelphys). Uterine anomalies are associated with several adverse pregnancy outcomes including preterm birth, hypertensive diseases of pregnancy, caesarean delivery, and fetal growth restriction [6–10]. Adverse outcomes are most common in women with unicornuate, bicornuate, and didelphys uterus, which are therefore classified as "major" fusion defects [10].

Large studies show that the greatest risk factor for spontaneous preterm birth is a prior preterm birth [11,12]. This also appears to be true in pregnancies already at increased risk for preterm birth, such as twin pregnancies [13]. It is currently unknown how prior pregnancy outcome modifies the risk of preterm birth in women with uterine anomalies. This is particularly relevant as historically the workup for and diagnosis of a uterine anomaly was only made after an adverse pregnancy outcome, such as preterm birth. It is uncertain if the reported incidences of adverse outcomes in women with uterine anomalies apply to women whose anomaly was found incidentally, or at least without a prior preterm birth. This information could assist with patient counseling, and potentially with selection of patients for studies regarding prevention of preterm birth in this population.

The objective of this study was to estimate the association between obstetric history and preterm birth in women with uterine anomalies, as well as a subset of women with major fusion defects (unicornuate, bicornuate, and didelphys). Our hypothesis was

CONTACT Nathan S. Fox nfox@mfmnyc.com Maternal Fetal Medicine Associates, PLLC, New York, NY, USA

Table 1. Baseline characteristics.

	Previous pregnancy preterm ($n = 53$)	Nulliparous ($n = 110$)	Previous pregnancy term ($n = 120$)	p^a
Maternal age (years)	31.2 ± 5.8	30.3 ± 7.0	31.9 ± 5.9	.173
Prepregnancy body mass index (kg/m^2)	24.5 ± 5.9	23.1 ± 4.3	23.9 ± 4.7	.186
White race	51 (96.2%)	97 (88.2%)	115 (95.8%)	.590
In vitro fertilization	10 (18.9%)	23 (20.9%)	12 (10.0%)	.060
Anticoagulation	4 (7.5%)	3 (2.7%)	4 (3.3%)	.283
Prior LEEP or cone biopsy	1 (1.9%)	2 (1.8%)	0 (0.0%)	.184
Chronic hypertension	0 (0.0%)	1 (0.9%)	1 (0.8%)	.617
Pregestational diabetes	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA
Cerclage	10 (18.9%)	1 (0.9%)	10 (8.3%)	.131
17-OH-progesterone	31 (58.5%)	2 (1.8%)	11 (9.2%)	<.001
Vaginal progesterone	2 (3.8%)	8 (7.3%)	5 (4.2%)	.845

Results reported as mean ± SD or *n* (%).
[a]Chi-square for trend or one-way ANOVA across all three groups.

that obstetric history would be significantly associated with the risk of preterm birth in this cohort.

Materials and methods

After Institutional Review Board approval was obtained, we reviewed the records of all patients with a singleton pregnancy and uterine anomaly ≥20 weeks delivered by a single maternal–fetal medicine practice between 2005 and 2016. The diagnosis of a uterine anomaly was made prepregnancy or after delivery either by a saline infusion sonohysterogram (SIS), magnetic resonance imaging (MRI), hysteroscopy, laparoscopy, or a combination of the above. Classification of uterine anomalies was made according to the 1988 American Fertility Society classification [14]. We considered the following uterine anomalies: arcuate, septate (intact and resected), unicornuate, bicornuate, t-shaped, and didelphys. We also identified a subgroup of patients with major fusion defects, defined as unicornuate, bicornuate, or didelphys uterus [10].

We divided all patients into three groups based on their pregnancy history: (1) prior preterm birth <37 weeks; (2) nulliparous; (3) prior term birth ≥37 weeks. In determining prior pregnancy history, we did not include any pregnancy losses prior to 20 weeks. For women with more than one prior pregnancy, we used the most recent birth ≥20 weeks in the main analysis. However, we reanalyzed the data defining the prior preterm birth group as any woman with a prior preterm birth at any time, even if not the most recent pregnancy. Baseline characteristics and pregnancy outcomes were obtained from our computerized medical record and were compared across the three groups. We performed the same analyses in the subgroup of patients with major fusion defects.

Patients in our practice with uterine anomalies routinely undergo first and second trimester ultrasound. The expected date of delivery was revised if the discrepancy was >5 days between the calculation from the last menstrual period and ultrasound up to 14-week gestation or >7 days if the dating ultrasound scan was performed after 14-week gestation. If the pregnancy was the result of *in vitro* fertilization (IVF), gestational age was determined from the date of embryo transfer. Patients were followed with serial ultrasounds estimating fetal weight approximately every four weeks, and measuring cervical length every 2–4 weeks from 16 to 32 weeks. However, if patients with a uterine anomaly had a history of a term birth, cervical length was not routinely measured.

Over the course of the study period, patients with a uterine anomaly and a prior spontaneous preterm birth were offered 17-alpha-hydroxyprogesterone caproate (17-OH-P) from 16 weeks until the sooner of 36 weeks or delivery. Counseling was individualized for women with a mixed history of term and preterm births, as well as for women with a history of late preterm birth (34 0/7 – 36 6/7 weeks). We do not routinely recommend cerclage for women with uterine anomalies except in exceptional situations such as a woman with prior preterm birth and a short cervical length <2.5 cm, or a woman with a dilated cervix. Women with a short cervical length and no indication for cerclage were offered vaginal progesterone.

To compare outcomes across the three groups we used the chi square test for trend to test categorical outcomes [15] and one-way ANOVA to test continuous outcomes. When only two groups were compared, we used chi square testing, Fisher's exact test, and Student's *t*-test, as appropriate (SPSS for Windows version 22.0, Armonk, NY, USA). The primary outcome was preterm birth <37 weeks. We also examined gestational age at delivery, preterm birth <35 weeks, and spontaneous preterm birth <37 weeks, defined as preterm birth resulting from preterm labor or premature rupture of membranes.

Table 2. Pregnancy outcomes.

	Previous pregnancy preterm ($n = 53$)	Nulliparous ($n = 110$)	Previous pregnancy term ($n = 120$)	p^a across three groups	p^b nulliparous versus previous pregnancy term
Gestational age at delivery	36.4 ± 2.4	38.3 ± 3.1	38.4 ± 2.6	<.001	.933
Preterm birth <37 weeks	32 (60.4%)	20 (18.2%)	19 (15.8%)	<.001	
Preterm birth <35 weeks	10 (18.9%)	10 (9.1%)	8 (6.7%)	.021	.494
Spontaneous preterm birth <37 weeks	21 (39.6%)	16 (14.5%)	10 (8.3%)	<.001	.137

Results reported as mean ± SD or *n* (%).
[a]Chi-square for trend or one-way ANOVA across all three groups.
[b]Chi-square or Student's *t*-test.

Table 3. Baseline characteristics for women with a major anomaly (unicornuate, bicornuate, and didelphys).

	Previous pregnancy preterm ($n = 28$)	Nulliparous ($n = 46$)	Previous pregnancy term ($n = 44$)	p^a
Maternal age (years)	30.4 ± 5.7	26.5 ± 5.2	30.1 ± 4.9	.001
Prepregnancy body mass index (kg/m^2)	25.0 ± 6.6	23.6 ± 5.1	25.0 ± 6.0	.431
White race	28 (100%)	43 (93.5%)	43 (97.7%)	.763
In vitro fertilization	5 (17.9%)	7 (15.2%)	5 (11.4%)	.434
Anticoagulation	2 (7.1%)	1 (2.2%)	0 (0.0%)	.068
Prior LEEP or cone biopsy	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA
Chronic hypertension	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA
Pregestational diabetes	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA
Cerclage	4 (14.3%)	0 (0.0%)	0 (0.0%)	.003
17-OH-progesterone	14 (50.0%)	0 (0.0%)	3 (6.8%)	<.001
Vaginal progesterone	0 (0.0%)	2 (4.3%)	3 (6.8%)	.170

Results reported as mean ± SD or *n* (%).
[a]Chi-square for trend or one-way ANOVA across all three groups

Results

We identified 283 women with the following uterine anomalies: 87 septate with resection (30.7%), 38 septate without resection (13.4%), 72 bicornuate (25.4%), 30 unicornuate (10.6%), 27 arcuate (9.5%), 16 didelphys (5.7%), 10 t-shaped (3.5%), and 3 unclassified (1.1%). There were 53 (18.7%) women with a prior preterm birth, 110 (38.9%) nulliparous women, and 120 (42.4%) women with a prior term birth. Baseline characteristics did not differ between the three groups including maternal age, prepregnancy body mass index (BMI), race, IVF, prior cervical excision, and medical complications (Table 1). The women with a prior preterm birth were more likely to have 17-OH-P therapy, as expected. A prior preterm birth was significantly associated with earlier gestational ages at delivery, and increased rates of preterm birth <37 weeks, <35 weeks, and spontaneous preterm birth <37 weeks (Table 2). When we compared nulliparous women to women with a prior term birth, there were no significant differences between the two groups (Table 2).

We then performed a subgroup analysis for the 118 women with a major uterine anomaly. There were 28 (23.7%) women with a prior preterm birth, 46 (39.0%) nulliparous women, and 44 (37.3%) women with a prior term birth. Baseline characteristics were similar between the groups, except that the nulliparous women were more likely to be younger (Table 3). Women with a prior preterm birth were significantly more likely to undergo cerclage placement and have 17-OH-P therapy, as expected. A prior preterm birth was significantly associated with earlier gestational ages at delivery, and increased rates of preterm birth <37 weeks, <35 weeks, and spontaneous preterm birth <37 weeks (Table 4). When we compared nulliparous women to women with a prior term birth, there were no significant differences between the two groups (Table 4).

When we reanalyzed our data defining the prior preterm birth group as women with a prior preterm birth at any time (not just the most recent pregnancy), our results did not differ. For example, the mean gestational age at delivery for women with a prior preterm birth at any time, nulliparous women, and only prior term births were 36.8 ± 2.7, 38.3 ± 3.1, and 38.6 ± 2.4 weeks, respectively, in all women and 36.2 ± 1.7, 37.8 ± 3.1, and 38.7 ± 1.8 weeks, respectively, in the women with a major uterine anomaly ($p < .001$ for both analyses).

Discussion

We found a significant association between prior preterm birth and recurrent preterm birth in women with uterine anomalies. The likelihood of preterm birth was

Table 4. Pregnancy outcomes for women with a major anomaly (unicornuate, bicornuate, and didelphys).

	Previous pregnancy preterm ($n = 28$)	Nulliparous ($n = 46$)	Previous pregnancy term ($n = 44$)	p^a across three groups	p^b nulliparous versus previous pregnancy term
Gestational age at delivery	35.9 ± 1.8	37.8 ± 3.1	38.3 ± 1.8	<.001	.338
Preterm birth <37 weeks	20 (71.4%)	12 (26.1%)	11 (25.0%)	<.001	.906
Preterm birth <35 weeks	7 (25.0%)	6 (13.0%)	2 (4.5%)	.012	.267
Spontaneous preterm birth <37 weeks	16 (57.1%)	9 (19.6%)	7 (15.9%)	<.001	.650

Results reported as mean ± SD or *n* (%).
[a]Chi-square for trend or one-way ANOVA across all three groups.
[b]Chi-square, Fisher's exact test, or Student's *t*-test.

three to four times higher in women with a prior preterm birth (60.4%), as opposed to nulliparous women (18.2%) and women with a prior term birth (15.8%). The results were similar among the subset of women with major uterine anomalies (71.4 versus 26.1 versus 25.0%). This was true even though 58.5% of these women received 17-OH-P and 18.9% received a cerclage. This indicates that despite treatment, women with a uterine anomaly and a prior preterm birth have a significant increased risk for recurrent preterm birth. Based on large studies of women with a prior spontaneous preterm birth and without a known uterine anomaly, progesterone supplementation decreases the recurrence of preterm birth compared to placebo by about 30% [16,17]. Our study suggests that its use in women with uterine anomalies requires further study.

Interestingly, a prior term birth did not appear to be "protective" against preterm birth as the likelihood of preterm birth did not differ between nulliparous women and women with a prior term birth. Prior studies suggest that pregnancy outcome is usually strongly associated with the previous pregnancy outcome [12,18], but this appears not to be the case in women with uterine anomalies and a prior term birth. Thus, women with a uterine anomaly and a prior term birth should not be considered low risk for preterm birth. In our cohort of women with a uterine anomaly and prior term birth, the likelihood of preterm birth was 15.8% overall and 25% in women with a major uterine anomaly.

Our findings could affect how we counsel patients with uterine anomalies regarding pregnancy outcome, and regarding the risks associated with future pregnancies. It may also affect antepartum surveillance or transfer to a higher level of care. However, it is currently unknown if and what surveillance or interventions improve outcomes in women with uterine anomalies and it is possible that our results may ultimately only influence prediction and counseling of risk. Studies that examine the effect of interventions on the risk of preterm birth in women with uterine anomalies should take into account the subjects' prior pregnancy history.

Pathways to preterm birth in women with uterine anomalies might differ from women without uterine anomalies, which may partially account for our findings. Lekovich et al. [19] looked at placental pathology after delivery in women with uterine anomalies and found that pathology in the placentas of preterm deliveries demonstrated higher rates of malperfusion, but not inflammation. This may suggest abnormal placentation as a source of preterm delivery in women with uterine anomalies. This is plausible as women with uterine anomalies are also at increased risk for fetal growth restriction and preeclampsia, which are both associated with abnormal placentation [9,10].

This study has several strengths. First, there were a large number of subjects and all had complete delivery records. Since we cared for all of these patients, we were able to rely on our own medical records, as opposed to using birth certificates or administrative databases. We are also confident that the diagnosis of uterine anomaly was correct, and the specific anomaly designation was accurate, given that we either reviewed the records of each patient, or made the diagnosis ourselves.

The study is limited by its retrospective design, but this analysis is not subject to randomization. Patients were managed differently based on their pregnancy history, but the increased surveillance and interventions in the group with a prior preterm birth likely had little effect on the primary outcome given the very high rate of recurrent preterm birth in this cohort. It is also possible we were underpowered for more rare outcomes, especially in the subgroup analyses.

In conclusion, in women with uterine abnormalities, a prior preterm birth is significantly associated with recurrent preterm birth. However, a prior term birth does not lower the risk of preterm birth as compared to nulliparous women. Further research is needed to assess the efficacy of interventions to prevent preterm birth in women with a uterine anomaly, particularly those with a prior preterm birth.

Disclosure statement

No potential conflict of interest was reported by the authors.

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