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ORIGINAL ARTICLE

Type of congenital uterine anomaly and adverse pregnancy outcomes

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Abstract

Objective: To estimate whether the severity of uterine anomaly is associated with the risk of adverse pregnancy outcomes.

Methods: Retrospective cohort study of patients delivered by one maternal fetal medicine group from 2005 to 2012. We included 158 patients with a singleton pregnancy and a uterine anomaly, as well as an equal number of randomly selected unexposed singleton pregnancies delivered by the same group. Patients with uterine anomalies were subdivided into those with major fusion defects (unicornuate, bicornuate and didelphys) and minor fusion defects (arcuate, septate and t-shaped).

Results: The incidence of adverse pregnancy outcomes increased across unexposed patients, patients with minor fusion defects and patients with major fusion defects. These included preterm birth < 37 weeks, preterm birth < 35 weeks, birth weight < 10th percentile, birth weight < 5th percentile, preeclampsia, malpresentation and cesarean delivery.

Conclusion: The incidence of adverse pregnancy outcomes and cesarean delivery is increased in patients with minor fusion defects and is further increased in patients with major fusion defects.

Keywords

Müllerian anomaly, preterm birth, preeclampsia, SGA, uterine anomaly

History

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Introduction

Congenital anomalies of the uterus, or congenital müllerian anomalies, include a spectrum of uterine abnormalities caused by abnormal embryologic fusion and canalization of the müllerian ducts to form a normal uterine cavity. These anomalies are often asymptomatic and unrecognized, but have a reported prevalence of approximately 2–4% in reproductive age women [1–4], and up to 5–25% in women with adverse reproductive outcomes [4,5]. The presence of a uterine anomaly appears to increase the risk of adverse pregnancy outcomes. Although limited by selection bias and small sample sizes, most of the data in singleton pregnancies suggest that patients with uterine anomalies are at increased risk for certain adverse pregnancy outcomes, including preterm birth, cesarean delivery and fetal growth restriction [6–11]. However, most studies compare outcomes between patients with a normal uterus to all patients with a uterine anomaly, regardless of type. However, the spectrum of uterine anomalies ranges from an arcuate uterus, which is a mild variant involving a slight midline septum and minimal fundal cavity indentation, to uterine didelphys on the opposite end of the spectrum, which involves complete failure of fusion resulting in two separate uteri. Within this broad spectrum lie other uterine anomalies ranging in severity of fusion defects including unicornuate uterus, bicornuate uterus, t-shaped uterus and septate uterus. In addition, some patients have a history of a uterine septum, but underwent total or partial surgical removal prior to pregnancy. Based on the current literature, it would be difficult to estimate the risk of adverse pregnancy outcomes in a patient with a specific uterine anomaly as it is unknown how the type of uterine anomaly affects the risk compared to other types. It may also be possible that patients with uterine anomalies could be subdivided into subgroups, such as those with a major fusion defect that essentially only have a unilateral horn for pregnancy, including unicornuate, bicornuate and didelphys, and those with a minor fusion defect, where the cavity is only partially altered, such as arcuate, septate and t-shaped. Finally, the current published studies do not look at several outcomes in the same population, including preterm birth, intrauterine growth restriction (IUGR), preeclampsia and gestational diabetes. The objective of this study is to estimate the association between uterine anomalies and adverse pregnancy outcomes based on the type/severity of uterine anomaly.

Materials and methods

After Institutional Review Board approval was obtained, a historical cohort of patients was obtained from patients in our private Maternal–Fetal Medicine practice between 2005 and 2012. Our initial search included all patients with singleton

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pregnancies ≥ 22 weeks delivered by our practice since 2005 (when our computerized database was created). Our study cohort included all patients with a uterine anomaly diagnosed prior to or during pregnancy. The diagnosis of a uterine anomaly was made prepregnancy either by a saline infusion sonohysterogram, magnetic resonance imaging, hysteroscopy, laparoscopy or a combination of the above. Some of the uterine anomalies were diagnosed in our practice; others were diagnosed by outside centers prepregnancy. For all patients with a diagnosis of a uterine anomaly made at an outside center, the medical records and imaging reports were reviewed to ensure accuracy of diagnosis. All uterine anomalies diagnosed during pregnancy were evaluated postpartum as well to confirm the diagnosis. Classification of uterine anomalies was made according to the 1988 American Fertility Society classification [12]. We considered the following uterine anomalies: arcuate, septate, unicornuate, bicornuate, t-shaped and didelphys. Patients with a uterine septum were further divided into those with an intact septum and those who underwent hysteroscopic resection prior to pregnancy. After initial inspection of our data, we divided all patients with a uterine anomaly into two groups: major fusion defects (unicornuate, bicornuate and didelphys) and minor fusion defects (septate, arcuate and t-shaped). For an unexposed group, we chose an equal number of randomly selected singleton pregnancies ≥22 weeks delivered by our practice over the study period.

Baseline characteristics and pregnancy outcomes were obtained from our computerized medical record and were compared across three groups: unexposed patients, patients with minor fusion defects and patients with major fusion defects. Patients in our practice routinely have first and second trimester ultrasound. The expected date of delivery was revised if the discrepancy was >5 d between the calculation from the last menstrual period and ultrasound scan up to 14 weeks gestation or >7 d if the dating ultrasound scan was performed after 14 weeks gestation. If the pregnancy was the result of *in vitro* fertilization (IVF), gestational age was determined from the date of embryo transfer. To define birth weight percentiles for gestational age, we used standard tables for singleton pregnancies [13]. Standard definitions were used for preeclampsia [14]. We looked at cesarean section rates in all patients as well in patients who attempted vaginal delivery. Patients planning on cesarean delivery (breech presentation, for example) who went into labor and underwent cesarean delivery were not considered as having attempted vaginal delivery, as they did not intend on a vaginal delivery.

In our practice, patients with uterine anomalies are typically followed with serial ultrasounds estimating fetal weight approximately every 4 weeks and measuring cervical length every 2–4 weeks. We also perform fetal fibronectin tests every 2–4 weeks from 22 to 32 weeks. If patients with a uterine anomaly have a history of a term birth, we do not routinely measure the cervical length or perform any fetal fibronectin tests in these patients.

To compare outcomes across the three groups of increasing severity (unexposed, minor fusion abnormality and major fusion abnormality), we used the chi square test for trend to test categorical outcomes [15] and one-way analysis of variance to test continuous outcomes. When we compared two groups, we used the chi-square test, Fisher's exact test and Student's *t*-test, as appropriate (SPSS for Windows 16.0, Chicago, IL).

Results

Over the course of the study period, we delivered 4473 singleton pregnancies ≥22 weeks, 158 of whom had a uterine anomaly, for an overall prevalence of 3.5%. Seven (4.4%) of the patients with a uterine anomaly were diagnosed during pregnancy and all were confirmed postpartum. Of the 158 patients with a uterine anomaly, the frequency of each specific anomaly in descending order of frequency was repaired septate uterus 50 (31.6%), bicornuate 46 (29.1%), unicornuate 16 (10.1%), intact septate 16 (10.1%), arcuate 14 (8.9%), t-shaped 10 (6.3%) and didelphys 6 (3.8%). One of the patients with a bicornuate uterus underwent metroplasty prior to pregnancy. Twelve (7.6%) patients with a uterine anomaly underwent cerclage placement during pregnancy.

The risk of preterm birth <37 weeks, birth weight <10th percentile for gestational age and birth weight <5th percentile for gestational age across all the subtypes of uterine anomalies, as well as for unexposed patients, are listed in Table 1.

We then divided the patients with uterine anomalies into two subgroups: major fusion defects (unicornuate, bicornuate and didelphys) and minor fusion defects (arcuate, septate and t-shaped). Baseline demographics across these two groups and unexposed patients are listed in Table 2. As expected, increasing severity of uterine abnormality was associated with a younger maternal age, decreased parity and a higher proportion of prior preterm birth and cesarean delivery. Other baseline characteristics were similar across the groups, including the prevalence of maternal medical conditions.

We compared pregnancy outcomes across the three groups, and the results are listed in Table 3. Comparing unexposed patients, patients with minor fusion defects and patients with major fusion defects, the gestational age at delivery decreased significantly, and the rate of overall preterm birth <37 weeks and <35 weeks increased significantly. When dividing preterm births into spontaneous (from preterm labor or premature rupture of membranes) and indicated (for maternal or fetal indications, such as growth restriction or

Table 1. Incidence of preterm birth and low birth weight percentiles, based on type of uterine anomaly.

	Unicornuate $N=16$	Bicornuate $N=46$	Didelphys $N=6$	Arcuate $N=14$	Septate, not repaired $N=16$	Septate, repaired $N=50$	T-shaped $N=10$	Control $N=158$
Preterm birth < 37 weeks	50.0%	39.1%	33.3%	7.1%	25.0%%	16.0%	20.0%	8.9%
Birth weight < 10th percentile	18.8%	28.3%	50.0%	21.4%	6.2%	12.0%	30.0%	3.8%
Birth weight < 5th percentile	6.2%	19.6%	33.3%	0%	0%	0%	10%	2.5%

Table 2. Baseline characteristics, based on the type of uterine anomaly.

	Unexposed $N = 158$	Minor fusion abnormality $N = 90$[a]	Major fusion abnormality $N = 68$[b]	p value[c]
Maternal age	33.2 ± 6.5	32.0 ± 6.2	29.2 ± 5.7	<0.001
IVF	9.5%	13.3%	16.2%	0.139
White race	94.3%	94.4%	95.6%	0.717
Parity				
0	29.1%	53.3%	47.1%	<0.001
1	25.9%	24.4%	33.8%	
2 or more	44.9%	22.2%	19.1%	
Prior term birth	65.2%	46.7%	52.9%	0.028
Prior preterm birth	15.8%	32.2%	38.2%	0.017
Prior cesarean delivery	27.8%	28.9%	45.6%	0.030
Fibroids	1.3%	8.9%	1.5%	0.412
Prior LEEP or cone	1.3%	0%	0%	0.203
On anticoagulation	3.2%	2.2%	4.4%	0.733
Chronic hypertension	2.5%	2.2%	4.4%	0.507
Preexisting renal disease, including absent kidney	0.6%	0.0%	2.9%	0.177
Prepregnancy BMI (kg/m^2)	24.2 ± 5.7	23.5 ± 4.3	25.1 ± 6.1	0.186
Prepregnancy obesity (BMI ≥ 30 kg/m^2)	10.1	11.1%	15.2%	0.310

Data are % or mean ± 1 SD.
[a]Arcuate, septate and t-shaped.
[b]Unicornuate, bicornuate and didelphys.
[c]Chi square for trend, or one-way ANOVA.

Table 3. Pregnancy outcomes, based on the type of uterine anomaly.

	Unexposed $N = 158$	Minor fusion abnormality $N = 90$[a]	Major fusion abnormality $N = 68$[b]	p value (trend across the three groups)[c]	p value (minor fusion abnormality versus unexposed)[d]	p value (major fusion abnormality versus minor fusion abnormality)[d]
Gestational age at delivery	39.1 ± 1.7	38.4 ± 2.9	37.2 ± 2.5	<0.001	0.034	0.005
Preterm birth < 37 weeks, overall	8.9%	16.7%	41.2%	<0.001	0.066	0.001
Preterm birth < 37 weeks, spontaneous	8.2%	11.1%	29.4%	<0.001	0.498	0.004
Preterm birth < 37 weeks, indicated	0.6%	5.6%	11.8%	0.001	0.025	0.160
Preterm birth < 35 weeks, overall	1.3%	6.7%	10.3%	0.002	0.028	0.411
Preterm birth < 35 weeks, spontaneous	0.6%	4.4%	5.9%	0.018	0.060	0.726
Preterm birth < 35 weeks, indicated	0.6%	2.2%	4.4%	0.055	0.299	0.652
Birth weight (g)	3289 ± 529	3176 ± 559	2775 ± 587	<0.001	0.056	<0.001
Birth weight < 10th percentile	3.8%	14.4%%	27.9%	<0.001	0.005	0.024
Birth weight < 5th percentile	2.5%	1.1%	17.6%	<0.001	0.656	<0.001
Preeclampsia	2.5%	2.2%	10.4%	0.016	0.999	0.014
Gestational diabetes	3.2%	3.3%	3.0%	0.964	0.999	0.902
IUFD	0.0%	1.1%	0.0%	0.716	0.363	0.999
Placenta previa (at delivery)	0.6%	4.4%	4.4%	0.055	0.137	0.999
Malpresentation	2.5%	16.7%	32.4%	<0.001	<0.001	0.024
Cesarean delivery (overall)	29.7%	45.6%	64.7%	<0.001	0.012	0.017
Cesarean delivery (labored)	10.5% (13/123)	14.3% (8/56)	24.1% (7/29)	0.060	0.461	0.259

Data are % or mean ± 1 SD.
[a]Arcuate, septate and t-shaped.
[b]Unicornuate, bicornuate and didelphys.
[c]Chi square for trend, or one-way ANOVA.
[d]Chi square, Fisher's exact or Student's t test.

preeclampsia), the rate of spontaneous preterm birth <37 weeks and <35 weeks increased significantly across the three groups. The rate of indicated preterm birth <37 weeks increased significantly across the three groups, and there was a statistical trend ($p = 0.055$) for indicated preterm birth <35 weeks, although this could have been due to lack of power for this particular outcome.

The birth weight decreased across all three groups, and the likelihood of small for gestational age (SGA, defined as a birth weight less than the 10th percentile and less than the 5th percentile) increased across all three groups. Similarly, the rate of malpresentation and preeclampsia increased across the three groups. The rate of gestational diabetes and intrauterine fetal demise did not increase across the three groups.

The rate of cesarean delivery increased across the three groups in all patients. In patients who labored, there was a statistical trend toward increasing risk of cesarean delivery across the three groups ($p = 0.060$). The indication for cesarean delivery among the seven patients with major fusion defects who labored was arrest of labor in three patients (43%) and nonreassuring fetal heart rate in four patients (57%). For the eight patients with minor fusion

defects who labored and underwent cesarean delivery, the indications were arrest of labor in five patients (63%) and nonreassuring fetal heart rate in three patients (37%).

The results of group-specific comparisons are shown in Table 3 as well. When comparing patients with minor fusion defects to unexposed patients, there was a significantly increased risk of overall preterm birth <35 weeks, indicated preterm birth <37 weeks, birth weight less than the 10th percentile, malpresentation and cesarean delivery, as well as an earlier mean gestational age at delivery. When comparing patients with major fusion defects to patients with minor fusion defects, there was a significantly increased risk of overall preterm birth <37 weeks, spontaneous preterm birth <37 weeks, birth weight less than the 10th percentile and less than the 5th percentile, preeclampsia, malpresentation and cesarean delivery, as well as an earlier mean gestational age at delivery and a smaller mean birth weight.

Discussion

In this study, we found that, in patients with uterine anomalies, the risk of adverse pregnancy outcomes was increased in patients with minor fusion defects (arcuate, septate and t-shaped) and further increased in patients with major fusion defects (unicornuate, bicornuate and didelphys). This was true in regards to overall preterm birth, spontaneous preterm birth, indicated preterm birth, low birth weight, SGA, preeclampsia, malpresentation and cesarean delivery. Others have shown that patients with uterine anomalies have an increased risk of these outcomes, but those studies lumped all patients with uterine anomalies together into one cohort. One meta-analysis by Chan et al. combined patient data from multiple prior studies and reported pooled risks of adverse outcomes based on the specific type of uterine anomaly [6]. However, the only third trimester pregnancy outcomes studied were preterm labor and malpresentation at delivery. Chan et al. did not report cesarean rates overall, in patients who labored, nor other adverse outcomes such as SGA, birth weight and preeclampsia. It would have been difficult to do so in this meta-analysis as most of the studies published prior did not report these outcomes, so they would not have data on these outcomes to pool. A recent study by Hua et al. used a single center ultrasound database and compared outcomes in 203 patients with uterine anomalies to 66 753 unexposed patients [11]. Hua et al. found that uterine anomaly was associated with preterm birth, cesarean delivery and IUGR (defined as a birth weight less than the 10th percentile). In our study, we confirmed these findings and had several other novel findings as well. First, we were able to demonstrate an increasing risk of these adverse outcomes with increasing severity of uterine anomaly, from minor fusion defects to major fusion defects. This is important as it confirms that even patients with minor abnormalities of the uterus are at increased risk of adverse outcomes, but also that patients with more severe defects are at an even higher risk. Second, we found an increased risk of birth weight less than the fifth percentile, in patients with a major fusion defect. Hua et al. only examined birth weight less than the 10th percentile, which would by definition be a more common outcome. Third, we found an increased risk of preeclampsia in patients with a major fusion defect. Hua et al. had a similar rate of preeclampsia in their uterine anomaly group (11.5%) as we did in ours (10.4%). However, their unexposed group had a higher prevalence of preeclampsia (8.0%) than we had in our unexposed group (2.5%), which could explain why we found a significantly higher rate of preeclampsia in patients with uterine anomalies but Hua et al. did not. Our patients with major fusion defects had a higher (but insignificant) rate of underlying renal disease, which could partially explain our findings. It is also possible that more patients in the major fusion defect group had underlying renal disease that was subclinical and unrecognized, as not all patients necessarily underwent renal evaluation prior to pregnancy, but these disorders are known to be higher among patients with uterine abnormalities [16,17].

Another novel finding in our study was the increased risk of cesarean delivery seen in patients with uterine anomalies, even in patients who attempted vaginal delivery. It is well-known that uterine anomalies increase the risk of malpresentation, which could partially explain an overall increased risk of cesarean delivery. However, even in our patients who labored and attempted vaginal delivery, there was a statistical trend toward an increased risk of cesarean delivery in patients based on the severity of uterine abnormality. Therefore, not only does a uterine anomaly increase the risk of cesarean delivery from causes such as malpresentation and placenta previa, it may also increase the risk of cesarean delivery in labor as well and more research is warranted as this is important information when counseling patients with these abnormalities.

Our decision to subdivide patients with uterine anomalies into subgroups can be seen as arbitrary, but in fact has scientific plausibility. Patients with a major fusion defect essentially have unilateral placental implantation, which could lead to functional exclusion of one uterine artery from the uteroplacental circulation, which is what was concluded by Leible et al. based on flow velocity waveforms obtained from the placental and nonplacental uterine arteries in patients with müllerian anomalies and unexposed patients [18]. In an animal model studied by Meyer et al., unilateral uterine horn ligation led to decreased placental size and weight, as well as increased IUGR [19]. This could explain why patients in our study with a major uterine anomaly were the only ones at risk for birth weight <5th percentile and preeclampsia, as these outcomes are more likely to be related to uteroplacental insufficiency. This categorization of uterine anomalies into major or minor fusion defects could potentially improve and simplify patient counseling regarding risk.

One could argue whether all uterine variants should even be considered abnormal. For example, arcuate uterus, which represents a small change in the fundal concavity, is considered by some to be a variant of normal. We chose to include arcuate uterus in our analysis due to the increased risk of certain adverse outcomes, namely second trimester loss and malpresentation at delivery, seen in a large meta-analysis by Chan et al. [6]. Furthermore, we chose to include patients with a resected uterine septum as it is unclear if septum resection improves outcomes not related to miscarriage, such as the ones we examined in this study. Müllerian developmental abnormalities may affect the functional, in addition to

the structural, alteration of the cervix and uterine musculature. Therefore, simple anatomical correction therefore may not reduce the adverse pregnancy outcomes beyond miscarriage. Indeed, we did find that patients with these minor uterine defects were at increased risk of several adverse outcomes compared to unexposed patients. We were underpowered to study the relative outcomes between patients with a present versus resected uterine septum and future research could focus on this interesting clinical question.

Strengths to our study include the large sample size from a single center, as well as our computerized database, which decreases the likelihood of incorrect outcome data, which is notoriously present in data derived from birth certificates. In addition, since we cared for all of these patients, we were able to accurately ascertain whether they attempted vaginal delivery or not, which allowed us to report rates of cesarean delivery in labor, as opposed to just cesarean rates overall. Our study is limited by all the limitations inherent to retrospective studies. Namely, since the diagnosis of uterine anomaly was known, there could have been ascertainment bias introduced into the dataset. Furthermore, some patients with uterine anomalies are specifically referred to our practice for a history of complications or other factors that could be confounding factors.

In conclusion, patients with uterine anomalies are at increased risk for numerous adverse pregnancy outcomes, including overall preterm birth, spontaneous preterm birth, indicated preterm birth, SGA, preeclampsia, malpresentation and cesarean delivery. This is true for patients with minor fusion defects, such as arcuate, septate and t-shaped uterus, and the risk is further increased in patients with major fusion defects, such as unicornuate, bicornuate and didelphys uterus.

Declaration of interest

The authors report no conflicts of interest.

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