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Original Research

Congenital uterine anomalies and perinatal outcomes: a retrospective single-center cohort study

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Congenital uterine anomalies result from the abnormal differentiation, migration, fusion and canalization of Mullerian ducts with a prevalence of 1-10% for unselected population, 2-8% for infertile women and 5-30% for women with a history of miscarriage. Uterine anomalies are implicated as cause of reduced fertility as well as early pregnancy loss. Moreover, their presence is related to an increased risk of preterm birth, abnormal fetal presentation, cesarean delivery, placental abruption and small-for-gestational age infants. The presented study aims to evaluate the correlation between congenital uterine anomalies and poor perinatal outcomes. This was a retrospective, single-center cohort study including 29 women with congenital uterine anomalies. The control group included 100 women hospitalized for delivery with normal uterine morphology. Primary perinatal outcome was preterm birth (delivery before the 37th week of gestation); secondary endpoints were fetus small for gestational age (SGA) (< 10th percentile weight) and fetal abnormal presentation (non-cephalic presentation at the end of pregnancy). Data are presented as median or frequency. Correlations were compared using Mann-Whitney or Pearson's chi square test. Statistical tests were considered significant if $P < 0.05$. Preterm birth, fetal abnormal presentation, small for gestational age fetuses were significantly higher ($P < 0.001$) in the congenital uterine malformations group. Congenital uterine anomalies are associated with poor perinatal outcomes; moreover, our study shows that type of malformations mostly associated with worse reproductive outcomes are the septate uterus and sub-septate uterus.

Keywords

Uterine anomalies; Reproduction; Fetal outcomes; Fertility; Preterm birth

1. Introduction

Congenital uterine anomalies result from the abnormal differentiation, migration, fusion, and subsequent canalization of Mullerian ducts during embryogenesis [1]. They have been reported to be implicated as a potential cause of reduced fertility and miscarriages [2–4]. Basing on anomalies in the embryological development process, the uterine malformations can be divided in unification defects of the Mullerian ducts (unicornuate, bicornuate or didelphys uterus), canalization defects for incomplete resorption of the midline septum (sub-septate or septate uterus), Mullerian agenesis and arcuate uterus [5]. Data from literature, demonstrated that the aforementioned anomalies are present in 1-10% of unselected population, 2-8% of infertile women and 5-30% of women with a history of miscarriage [6]; however, the prevalence rate is uncertain due to the application of several diagnostic methods such as hysterosalpingography, hysteroscopy, laparoscopy, magnetic resonance imaging and three-dimensional sonography. In the same view, the use of three different classification systems developed by the American Society of Reproductive Medicine (ASRM, 2006) [7], the European Society of Human Reproduction and Embryology (ESHRE, 2013) and the European Society for Gynecological Endoscopy (ESGE, 2013) does not permit to establish a unique consensus about the prevalence of these malformations [2]. Moreover, uterine anomalies are often asymptomatic and accidentally diagnosed during ultrasounds for other gynecological pathologies, assessment of tubal patency or pregnancy [8, 9]. Moreover, they may also be recognized at delivery during spontaneous or cesarean section [10]. The presence of congenital uterine alterations represents a potential cause of infertility, recurrent pregnancy loss, preterm delivery, fetal malpresentation as well as small-for-gestational age infants, with greater effects being evident in women with more profound defects [11]. The presented study focused on the assessment of the perinatal outcomes in women affected by congenital uterine anomalies.

2. Materials e methods

2.1 Study design

We conducted a retrospective single-center cohort study including all consecutive women with congenital uterine anomalies attending the Gynecology and Obstetrics department of our Hospital from December 2010 to March 2020.

Table 1. Patients baseline characteristics.

	Uterine anomalies (N = 29)	Control Group (N = 100)	*P*-value
Age	29.4 ± 12.18 (18.40)	28.2 ± 19.03 (16-40)	0.6[a]
Gestational week	37 ± 2.16 (30-41)	39 ± 5.51 (34-41)	< 0.001[a]
BMI	25 ± 1.13 (21-26)	24 ± 7.19 (20-25)	0.5[a]
Ethnicity			
Caucasian	27 (93.1%)	96 (96%)	
Nigerian	3 (6.9%)	4 (4%)	0.3[b]
Smoking			
Yes	25 (86%)	85 (85%)	
No	3 (13%)	15 (4%)	0.7[b]
Preterm birth	12 (41.38%)	4 (4%)	< 0.001[b]
SGA	11 (37.93%)	9 (9%)	< 0.001[b]
Foetal Malpresentation	11 (37.93%)	2 (2%)	< 0.001[b]

Values are expressed as mean (SD). Values are expressed as number (n) and percentage (%). [a]Mann Whitney test. [b]Pearson Chi squared test.

2.2 Study population

A total of 29 women with congenital uterine anomalies were identified and were selected on the basis of the American Society of Reproductive Medicine (ASRM) classification (Table 1). The control group included 100 women hospitalized for delivery with normal uterine morphology at ultrasound, recruited in the same hospital during the same period. All data were acquired by reviewing medical records. All the women enrolled in the study subscribed an informed consent and met the following inclusion criteria: history of one or more pregnancies or current pregnancy with diagnosis of uterine anomalies. Women who have never had confirmed pregnancy by beta-HGC with first trimester ultrasound and who did not have specific diagnosis of uterine malformations, who underwent ART cycles and who experienced at least 1 miscarriage, were excluded, in contrast with previous studies [12].

2.3 Uterine anomalies selection

The uterine anomalies were classified using a single, well-defined system known as the modified ASRM classification system in order to provide a more reliable evidence of uterine anomalies prevalence. According to this system, uterine anomalies, consist of uterus didelphys (two external uterine orifices and two uterine bodies), bicornuate uterus (normal caudal part of the uterus and bifurcated cranial part), complete or incomplete septate uterus (normal external surface, two uterine cavities and one or two external uterine orifices), arcuate uterus (a concave dimple in the uterine fundus within the cavity), unicornuate uterus (one uterine endometrial cavity deviated to the right or left side), respectively.

2.4 Main outcome measures

The primary aim of this study was to evaluate the correlation between congenital anomalies and preterm birth (delivery before the 37th week of gestation) [13]; secondary outcomes were fetus small for gestational age (SGA) (< 10th percentile weight), fetal abnormal presentation (non-cephalic presentation at the end of pregnancy).

3. Statistical analysis

Continuous data (age and gestational week) were presented as median (interquartile range) or mean ± standard deviation. Categorical data (multiparity, preterm birth, fetal malpresentation and SGA) were analyzed using the Pearson's chi square test. The association congenital anomalies with preterm birth, after adjusting for potential confounders, was examined by multivariate linear regression. All covariates (women age, gestational week, BMI and ethnicity) were simultaneously entered to the multivariate linear regression model. The assumptions for the final model were successfully tested. All statistical tests used a two-tailed α of 0.05. All data were calculated using SPSS 17 software (SPSS Inc., Chicago, IL, USA).

4. Results

4.1 Patient characteristics

A total of 29 patients with congenital uterine anomalies (22.5%) and 100 patients with normal uterine morphology (77.5%) were included. The prevalence of didelphys and bicornuate uterus was respectively 10% and 48%; while 20% of the women presented complete septate uterus and 14% incomplete septate uterus. Unicornuate and arcuate uterus had the same percentage (3%). Patients' age was similar between the uterine anomalies group and the control group, while the gestational week was significantly lower in the uterine anomalies group than in controls (37 ± 2.16 vs 39 ± 5.51, $P < 0.001$). BMI value, ethnicity and the percentage of smokers did not show any statistical difference between the two groups.

4.2 Pregnancy outcome: congenital anomalies vs control

Overall, the 29 women with uterine anomalies had significantly higher complication rates compared to the control group: preterm birth, fetuses in a non-cephalic posi-

Table 2. Correlation between congenital uterine anomalies and reproductive outcomes.

	Didelphys uterus	Bicornuate uterus	Complete septate uterus	Uncomplete septate uterus	Control group	*P value*
Preterm Birth	66.7%	35.7%	50%	50%	4%	< 0.001
Foetal Malpresentation	0%	50%	33.3%	50%	2%	< 0.001
SGA	33.3%	35.7%	50%	50%	9%	< 0.001

Values are expressed as number percentage (%). Pearson Chi squared test.

tion and newborns with a weight below the 10th percentile were significantly higher in the congenital uterine anomalies group than in the counterparts (41.38% vs 4% of the control group, $P < 0.001$, 37.93% vs 2%, $P < 0.00$, 37.93% vs 9%, $P < 0.001$, respectively). Preterm birth occurred more frequently among women with didelphys uterus (66.7%) than in those with bicornuate uterus (35.7%) and canalization defects (50%). The association with the fetal malpresentation seems to be stronger in women with bicornuate (50%), incomplete (50%) or complete septate uterus (33.3%), than in those with didelphys uterus. At the end of pregnancy, fetus small for gestational age occurred in 33.3% of didelphys uterus, 35.7% of bicornuate uterus and 50% of complete and incomplete septate uterus (Table 2).

4.3 Multivariate regression analysis

Multivariate regression analysis revealed that lower age, the condition of smoker and the Caucasian ethnicity had not a significant preterm birth (CI = 0.98-1.02, 1.26-1.32, 0.99-1.03, respectively; $P = 0.075$, 0.065, 0.077, respectively) (Table 3). On the other hand, the lower gestational week and the presence of congenital anomalies was significantly associated with preterm birth (CI = 0.92-0.94,1.08-1.46, $P = < 0.001$, < 0.001, respectively) (Table 3).

Table 3. Multivariate logistic regression: outcome Preterm birth, predictors: age, gestational week, ethnicity, smoking, congenital anomalies.

	Odd Ratio	*P* values	95% CI	
Age	1.03	0.075	0.98	1.02
Gestational week	0.94	**< 0.001**	0.92	0.94
Ethnicity	1.01	0.077	0.99	1.03
Smoking	1.28	0.065	1.26	1.32
Congenital anomalies	1.25	**< 0.001**	1.08	1.46

5. Discussion

The results of our retrospective study demonstrated that uterine congenital anomalies had a significant negative effect on perinatal outcomes including preterm birth, fetal malpresentation at the end of the gestation and SGA. In particular, women with canalization defects, such as the complete and incomplete septate uterus, showed the worst reproductive outcomes, with a higher incidence of preterm birth and SGA [14], while patients with bicornuate uterus reported the highest rate of fetal malpresentation. Our results support previous series [15–17] and confirmed that the different types of Mullerian anomalies were individually associated with different obstetrics outcomes at varying severity degrees, with higher incidence of the worst outcomes in patients with more severe malformations [18]. Although the association between defects of canalization and the poor reproductive outcomes seems to be widely supported by scientific evidence, its pathophysiological process deserves future confirmations.

In this context, scientific background described that uterine septum consisted of a fibrous muscle tissue with poor vascularization. This uterine cavity alteration determines local uterine contractions, leading to preterm premature rupture of membranes and preterm birth [19–21] or difficult decidualization and implantation, with smaller uterine cavity and, thus, increased risks of SGA and miscarriages [22–25]. In this view, it would be interesting to investigate the association between septate uterus and miscarriage. Indeed, septate uterus is the only congenital uterine anomaly which, if surgically corrected with minimally invasive intervention such as hysteroscopic septum removal, may determine an improvement in reproductive outcomes. According to this, the largest series reported so far, showed a significant decrease in the early miscarriage rate from 89.6% to 12.4% after hysteroscopic septum removal, as well as an increase in term of delivery rate from 1.4% to 74.4% [26]. With regards to unification defects, such as bicornuate, unicornuate and didelfis uterus, their effects on perinatal outcomes depend on the type of anomaly. Our results reported that women with bicornuate and unicornuate uterus had an elevated risk of fetal malpresentation and SGA, while patients with the didelphys uterus showed high risk of preterm birth and SGA. Given this, our results are partially in accord with those of previous studies which reported that uterine unification negatively influenced pregnancy in particular, bicornuate and unicornuate uterus were associated with an increased risk of preterm birth and fetal malpresentation, whereas didelphys uterus showed a mild increased risk of preterm birth [27, 28]. The strength of our study relies on the accurate selection process of patients with uterine anomalies. However, limitations do exist and should be considered when interpreting the results, indeed, uterine abnormalities may be underestimated especially during pregnancy and, in general, the diagnosis of arcuate uterus may be overlooked for its minimally altered uterine cavity.

6. Conclusions

Congenital uterine anomalies, related to Mullerian development defects, are not so rare as supposed. Our study high-

lighted that congenital uterine anomalies are associated with poor perinatal outcomes. Complete and incomplete septate uterus malformations are associated with the worst perinatal outcomes. In this context, due to the consistent improving in minimally invasive and resolutive surgical techniques during the last two decades [29], it is reasonable to auspicate for this approach, in order to ameliorate reproductive and perinatal outcomes.

Ethics approval and consent to participate

Ethics approval was not required due to the observational/retrospective nature of the study. Written informed consent has been obtained by all the patients included in the study.

Author contributions

EZ and RA designed the study and wrote the manuscript. RA is responsible for data collection. EZ and LMDG provide the statistical analysis. FDG, GCM, FAG, SC, MCC and MP critically commented and substantially revised the manuscript. All authors participated in drafting the manuscript and approved the final version.

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Conflict of interest

The Authors declare that they have no conflict of interest.

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