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Reproductive and neonatal outcomes in women with unicornuate uterus: a population-based study

Abstract

Objective: To investigate reproductive and neonatal outcomes in women with unicornuate uterus.

Study design: Data from the Health Care Cost and Utilization Project-Nationwide Inpatient Sample database were extracted from 2010 through 2014 to create a delivery cohort using ICD-9 codes. Code 752.33 was used to identify cases with unicornuate uterus and reproductive outcomes were compared to pregnancies without unicornuate uterus. A multivariate logistic regression model was used to adjust for statistically significant variables (P-value<0.05).

Results: Among 3,850,226 deliveries during the study period, 802 women had unicornuate uterus. Patient with unicornuate uterus were more likely to be older (P<0.001), have thyroid disease (P<0.001), previous Caesarean section (P<0.001), and to have had in-vitro fertilization (IVF) (P<0.001).

The risk of gestational diabetes, pregnancy induced hypertension, gestational hypertension and preeclampsia were significantly greater in the unicornuate uterus group relative to controls, after controlling for baseline risk factors; aOR 1.32 [95% CI 1.03–1.71], aOR 1.46 [95% CI 1.16–1.85], aOR 1.16 [95% CI 1.22-2.28] and aOR 1.70 [95% CI 1.24-2.32], respectively.

Also, the rates of preterm delivery, preterm premature rupture of membranes and caesarean section were higher in the unicornuate uterus group compared to controls after controlling for confounding factors, aOR 3.83 (95% CI 3.19–4.6), aOR 5.11 (95% CI 3.73–7.14) and aOR 11.38 (95% CI 9.16–14.14) respectively.

At birth, 11.1% and 2.6% of neonates were small for gestational age in the unicornuate uterus and the control groups, respectively, aOR 4.90, (95% CI 3.87-6.21).

Conclusion: Women with unicornuate uterus are at higher risk for pregnancy complications, preterm delivery and having small for gestation age neonates. Women with known unicornuate uterus may benefit from increased surveillance to prevent and/or decrease maternal and neonate morbidity and mortality.

Keywords: unicornuate uterus, hemi-uterus, congenital uterine anomalies, mullerian dysgenesis, reproductive outcomes

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Introduction

Unicornuate uterus represents a congenital anomaly resulting from arrested development of one of the two Müllerian ducts during embryogenesis with a reported prevalence of approximately 0.03% to 0.1% and representing 5% to 20% of all Müllerian anomalies.[1] Differences in unicornuate uterine dysgenesis were classified in 1988 by the American Society of Reproductive Medicine (ASRM) based on the type of rudimentary horn present.[2] These include communicating, non-communicating, no cavity, or no horn. In 2013, the European Society of Human Reproduction and Embryology together with the European Society for Gynaecological Endoscopy (ESHRE/ESGE) proposed a classification system based on the level of deviation from normal anatomy and further subdivided based on associated cervical or vaginal abnormalities; a distinguishing entity of the ESHRE/ESGE classification.[3] At present, its pathogenesis remains elusive, however, due to the nature of the Müllerian duct malformation, multifactorial and polygenic circumstances in-utero are favored over genetic inheritance as causative factors.[4]

Women are typically diagnosed with a unicornuate uterus during routine evaluation of infertility, early pregnancy loss and/or adverse pregnancy outcomes by imaging or laparoscopic and/or hysteroscopic examination or during adolescence as a result of pain from retrograde menstruation. However, many women commonly experience delays in diagnosis which is attributed to menses associated pain.[6,7] At present, diagnostic modalities include hysterosalpingography, ultrasonography, magnetic resonance imaging (MRI) and more recently, endoscopy including laparoscopy and hysteroscopy.[8,9]

With a prevalence of 0.1% in the general population and 0.5% among infertile women, unicornuate uterus remains critical to evaluate its associated impact on affected patients.[10] Patients with unicornuate uterus experience greater gynecological and obstetrical adverse events including, but not limited to, infertility, early pregnancy loss and/or preterm delivery, as well as other pathologic conditions such as endometriosis or hematometra.[11]

Treatments for women with this uterine anomaly lack a standardized approach given the paucity of available evidence and existing

literature derived predominantly from case reports or small case series with opinion-based treatment methods and low-quality evidence.[12] Current management strategies depend on the subclassification of the unicornuate uterus and include a hemi-hysterectomy or reconstructive laparotomic or laparoscopic metroplasty, with the goal of providing symptomatic relief and improving gynecological and reproductive outcomes.[13]

Given the limited knowledge from published literature pertaining to fertility, pregnancy, and maternal and neonatal outcomes, the present study aims to use a population database to determine the association of unicornuate uterus with reproductive and neonatal outcomes, and to provide guidance on appropriate surveillance strategies to prevent and/or decrease the risk of associated maternal, fetal and neonatal adverse outcomes.

Materials and methods

A retrospective population-based study was conducted utilizing data from the Health Care Cost and Utilization Project-Nationwide Inpatient Sample database (HCUP-NIS) over 5 years from 2010 through 2014.[14] The HCUP-NIS is the largest inpatient sample database in the United States, comprising hospital inpatient stays submitted by hospitals throughout the entire country. Each year, the database provides information relating to 7 million inpatient stays, including patient characteristics, diagnosis and procedures, and data provided are taken as representative of more than 97% of inpatient discharges from community hospitals. The HCUP-NIS database includes hospital inpatient information from 48 of 50 US states, as well as the District of Columbia. This database, therefore, represents 96% of the American population in a geographical sense. Twenty percent of hospital admissions across these regions are included in the database. This study used exclusively publicly accessible, anonymized data; hence, according to articles 2.2 and 2.4 of Tri-Council Policy statement (2010), institutional review board approval was not required.

Inclusion criteria included pregnancies resulted in delivery or maternal death. Exclusion criteria were deliveries before 2010 or after 2014 and admissions that did not result in deliveries or maternal death. Delivery records were extracted between 2010 and 2014 inclusive using international classification of diseases, ninth edition, Clinical Modification (ICD-9-CM) diagnostic codes: 634x-679x, V22x, V23x, or V27x, and ICD-9-CM procedural codes: 72x-75x. We used ICD-9-CM codes: 650x, 677x, or 651x-676x, and ICD-9-CM procedure codes: 72x, 73x, 74.0, 74.1, 74.2, 74.4 or 74.99 for admissions that resulted in a delivery or a maternal death. A sub analysis was performed within this group and all women with a stated diagnosis of unicornuate uterus were identified using ICD-9 diagnostic code 752.33 which primarily appeared in the database in 2010, guiding our chosen study period. The remaining deliveries were categorized as non-unicornuate uterus and comprised the reference or control group.

ICD-9 codes were also used to identify demographic characteristics, pregnancy and delivery, and neonatal outcomes of all women in the study population. Baseline patient characteristics included age, race, income, insurance type, hospital type, previous caesarean section, multiple gestation, smoking history, BMI status (obese versus non-obese), pre-existing hypertension (HTN), pre-existing diabetes, and pre-existing thyroid disease.

Pregnancy events included gestational diabetes, placenta previa and hypertensive disorders of pregnancy as a group in total and individually as gestational hypertension, preeclampsia, eclampsia, and preeclampsia and eclampsia superimposed on hypertension.

Delivery data included preterm delivery, preterm premature rupture of membrane (PPROM), abruption placenta, chorioamnionitis, mode of delivery, maternal infection, peripartum hysterectomy, blood transfusion, venous thromboembolism (VTE), and maternal death. Maternal infections consisted of chorioamnionitis, septicemia during labor, postpartum endometritis, septic pelvic, or peritonitis. VTE included deep vein thrombosis (DVT) and pulmonary embolism (PE) during pregnancy, intrapartum or in the postpartum period. The neonatal outcomes assessed included small for gestational age (SGA), congenital anomalies and intrauterine fetal demise (IUFD).

Statistical analysis

We determined the prevalence and compared the demographic and clinical characteristics of women with and without unicornuate uterus using Chi-square test. Logistic regression analyses were conducted to explore associations between unicornuate uterus and maternal and neonatal obstetrical outcomes through the estimation of odds ratio (OR) and 95% confidence intervals (CI). The regression models were adjusted for potential confounding effects of maternal demographic, pre-existing clinical characteristics, and concurrently occurring characteristics. All analyses were performed using SPSS 23.0 (IBM Corporation, Chicago, USA) software for all analyses.

Ethics and institutional review

According to articles 2.2 and 2.4 of Tri-Council Policy statement (2010), institutional review board approval was not required.

Results

Among 3,851,028 deliveries, 802 (21/100 000 births or 0.021%) women were identified to have a diagnosis of a unicornuate uterus. Since the introduction of the diagnosis of unicornuate uterus in the database in 2010, it appears that there was a significant increase in the prevalence, likely due to incomplete recording, from 4.74 to 25.40 per 100,000 births and remained stable thereafter (Figure 1).

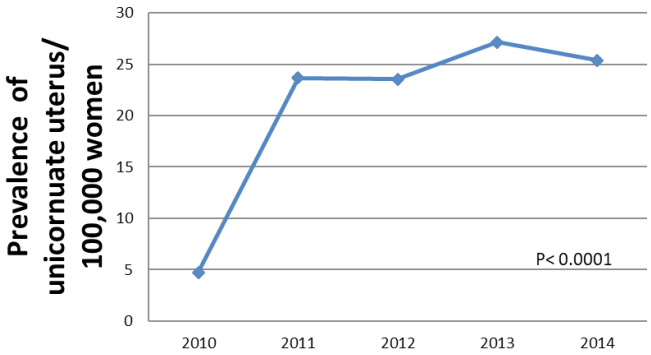

Figure 1 Prevalence Unicornuate uterus among women who gave birth between 2010 and 2014.

Baseline maternal demographic data and clinical characteristics are presented in Table 1. Women with a unicornuate uterus were found to be older, of Caucasian descent, have higher income, had a private insurance plan, had previously undergone a caesarean section, in-vitro fertilization (IVF), and had history of thyroid disease compared with controls (P<0.0001, Table 1).

With regards to pregnancy outcomes, patients with unicornuate uterus were shown to have a significantly greater incidence of pregnancy-induced hypertension (11.3%), gestational hypertension (5.1%), preeclampsia (5.4%) and gestational diabetes mellitus (9.1%), relative to controls (8%, 3.7 %, 3.6%, 6.5%, respectively). These

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associations were demonstrated and confirmed following controlling for confounding effects (age, race, plan type, income quartiles, obesity, previous caesarean section, chronic hypertension, thyroid disease and IVF) (Table 2). No significant differences were observed within the unicornuate group relative to the controls pertaining to eclampsia, preeclampsia and eclampsia superimposed hypertension, or placenta previa, following controlling for sociodemographic and clinical characteristics.

Table 1 Maternal characteristics of all patients (N=3 851 028) with and without unicornuate uterus: IVF-In vitro fertilization

Characteristics	Unicornuate uterus N= 802 (%)	No unicornuate uterus N= 3 850 226 (%)	P-value
Age (years) (18-38)			
<25	206 (25.7)	1,378,381 (35.8)	<0.0001
25-34	429 (53.5)	1,898,161 (49.3)	
≥35	167 (20.8)	573,684 (14.9)	
Race			
White	577 (71.9)	2,036,770 (52.9)	<0.0001
Black	40 (5.0)	562,133 (14.6)	
Hispanic	111 (13.9)	827,798 (21.5)	
Asian and Pacific	36 (4.5)	207,912 (5.4)	
Native American	1 (0.1)	30,802 (0.8)	
Other	37 (4.6)	184,811 (4.8)	
Income quartiles			
≤ $39 000	145 (18.1)	1,066,512 (27.7)	<0.0001
$39 000-47 999	198 (24.7)	962,557 (25.0)	
$48 000-62 999	215 (26.8)	970 257 (25.2)	
≥$63 000	244 (30.4)	850,900 (22.1)	
Plan type			
Medicare	4 (0.5)	26,952 (0.7)	<0.0001
Medicaid	245 (30.5)	1,690,249 (43.9)	
Private Insurance	513 (64.0)	1,917,413 (49.8)	
Self-pay	16 (2.0)	100,106 (2.6)	
No charge	2 (0.2)	3,850 (0.1)	
Other	22 (2.7)	111,656(2.9)	
Hospital type			
Rural	107(13.4)	542,882(14.1)	0.68
Urban	695 (86.6)	3,307,344 (85.9)	
Obese (BMI > 30)	46 (5.7)	211,762 (5.5)	0.8
Previous CS	307 (38.3)	658,389 (17.1)	<0.0001
Smoking during pregnancy	39 (4.9)	211,762 (5.5)	0.45
Chronic HTN	24 (3.0)	84,705 (2.2)	0. 11
Pregestational DM	8 (1.0)	3,850 (1.0)	0.91
Recreational drugs	8 (1.0)	3,850 (1.6)	0.15
Thyroid disease	53 (6.6)	119,357 (3.1)	<0.0001
HIV	0 (0.0)	820 (0.0)	1
IVF	14 (1.7)	7,700 (0.2)	<0.0001
Multiple gestation	17 (2.1)	65,454 (1.7)	0.38

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Table 2 Pregnancy outcomes of women with and without unicornuate uterus

Pregnancy outcomes[a]	Unicornuate uterus	No unicornuate uterus	Crude OR (95% CI)	Adjusted OR (95% CI)	Adjusted p-value
HDP	91 (11.3)	308,018 (8)	1.467 (1.18 - 1.82)	1.462 (1.16 - 1.85)	0.002
Gestational hypertension	41 (5.1)	142,458 (3.7)	1.42 (1.04 -1.95)	1.16 (1.22 – 2.28)	0.001
Preeclampsia	43 (5.4)	138,608 (3.6)	1.43 (1.05 – 1.95)	1.69 (1.24 - 2.32)	0.001
Eclampsia	0 (0.0)	3,850 (0.1)	0.000 (0.000-)	0.000 (0.000 -)	0.1
Preeclampsia/Eclampsia superimposed HTN	10 (1.2)	231,014 (0.6)	1.973 (1.06 – 3.68)	2.26 (1.21 - 4.22)	0.01
GDM	73 (9.1)	250,265 (6.5)	1.45 (1.139 – 1.84)	1.32 (1.03 - 1.70)	0.03
Placenta previa	6 (0.7)	231,014 (0.6)	1.31 (0.59 – 2.93)	0.95 (0.39 - 2.29)	0.91

HDP, hypertensive disorders of pregnancy; HTN, hypertension; GDM, gestational diabetes mellitus

a- Pregnancy outcomes: Adjusted for age, race, plan type, income quartiles, obesity, previous caesarean section, chronic hypertension, thyroid disease and IVF

With regards to delivery outcomes, all outcomes were adjusted for age, race, plan type, income quartiles, obesity, previous caesarean section, chronic hypertension, thyroid disease, IVF, hypertensive disorders of pregnancy, gestational hypertension, preeclampsia, preeclampsia and eclampsia superimposed HTN and gestational diabetes. Preterm premature rupture of the membranes (PPROM), preterm delivery, and caesarean section were found to be statistically greater in the unicornuate uterus group, relative to controls, with an adjusted odds ratio of 5.11 (95% CI 3.73–7.14), 3.83 (95% CI 3.19–4.6) and 11.61 (95% CI 9.34–14.44), respectively. Furthermore, the incidence of operative vaginal delivery was lower in the unicornuate group relative to controls aOR 0.35(95% CI 0.18–0.65). No cases of maternal death or pulmonary embolism were reported within the unicornuate uterus group.

With regards to neonatal outcomes, 11.1% of neonates were found to be small for gestational age in the unicornuate uterus group versus 2.6% in controls (aOR 4.90, 95% CI 3.87–6.21) (Table 3). Moreover, 0.1% of women within the unicornuate uterus group experienced intra-uterine fetal death compared to 0.4% in controls (P=0.33). These outcomes were adjusted for age, race, plan type, income quartiles, obesity, previous caesarean section, chronic hypertension, thyroid disease, IVF, hypertensive disorders of pregnancy, gestational hypertension, preeclampsia, preeclampsia and eclampsia superimposed HTN and gestational diabetes. A detailed summary of pregnancy, neonatal and maternal outcomes, along with associated odds ratios, are presented in Tables 4,5.

Table 3 Delivery outcomes of women with and without unicornuate uterus

Delivery outcomes[a]	Unicornuate uterus	No unicornuate uterus	Crude OR	Adjusted OR	Adjusted p-value
			(95% CI)	(95% CI)	
PPROM	42 (5.2)	46,203 (1.2)	4.74 (3.47 - 6.47)	5.11 (3.73 - 7.14)	<0.0001
Preterm delivery	168 (20.9)	254,115 (6.6)	3.74 (3.16 - 4.44)	3.83 (3.19 - 4.60)	<0.0001
Abruptio placenta	13 (1.6)	42,352 (1.1)	1.53 (0.88 - 2.65)	1.47 (0.81 - 2.67)	0.21
Chorioamnionitis	12 (1.5)	73,154 (1.9)	0.77 (0.44 - 1.37)	1.01 (0.56 - 1.84)	0.96
Spontaneous Vaginal Delivery	106 (13.2)	2,402,541 (62.4)	0.09 (0.07- 0.11)	0.10 (0.08 – 0.13)	<0.0001
Operative vaginal delivery	11 (1.4)	207,912 (5.4)	0.24 (0.13 - 0.44)	0.35 (0.18 - 0.65)	0.001
CS	685 (85.4)	1,266724 (32.9)	11.93 (9.80 - 14.51)	11.61 (9.34 - 14.44)	<0.0001
Hysterectomy	4 (0.5)	3,850 (0.1)	5.05 (1.89 - 13.49)	2.78 (0.89 - 8.66)	0.08
PPH	24 (3.0)	115,507 (3.0)	0.98 (0.66 – 1.48)	1.06 (0.69 - 1.62)	0.8
Wound complications	7 (0.9)	11,551 (0.3)	2.63 (1.25 - 5.53)	1.09 (0.41 - 2.93)	0.85
Maternal Death	0 (0.0)	249 (0.0)	0.000 (0.000 -)	0.000 (0.000 -)	0.1
Transfusion	15 (1.9)	46,203 (1.2)	1.57 (0.94 – 2.62)	1.42 (0.82 - 2.47)	0.21

PPROM, preterm premature rupture of membranes; CS, caesarian section; PPH, postpartum hemorrhage

a- Delivery Outcomes: Adjusted for age, race, plan type, income quartiles, obesity, previous caesarean section, chronic hypertension, thyroid disease, IVF, hypertensive disorders of pregnancy, gestational hypertension, preeclampsia, preeclampsia and eclampsia superimposed HTN and gestational diabetes

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Table 4 Miscellaneous maternal outcomes in women with and without unicornuate uterus

Miscellaneous Outcomes[a*]	Unicornuate uterus	No unicornuate uterus	Crude OR (95% CI)	Adjusted OR (95% CI)	Adjusted p-value
Maternal infection	13 (1.6)	88,555 (2.3)	0.71 (0.41 - 1.23)	0.84 (0.46 - 1.53)	0.58
DVT	1 (0.1)	3,850 (0.1)	3.11 (0.44 – 22.09)	3.01 (0.43 – 22.05)	0.26
PE	0 (0.0)	755 (0.0)	0.000 (0.000 -)	0.000 (0.000 -)	0.99
VTE	1 (0.1)	3,850 (0.1)	2.16 (0.30 - 15.39)	2.19 (0.31- 15.58)	0.44
DIC	3 (0.4)	7,700 (0.2)	1.53 (0.49 – 4.74)	1.46 (0.47 – 4.56)	0.51

DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism; DIC, disseminated intravascular coagulation

a- Miscellaneous maternal outcomes were adjusted for age, race, medical insurance plan type, income quartiles, obesity, previous Caesarian section, chronic hypertension, thyroid disease, IVF, hypertensive disorders of pregnancy, gestational hypertension, preeclampsia, preeclampsia/eclampsia superimposed hypertension and gestational diabetes

Table 5 Neonatal outcomes in women with and without unicornuate uterus

Neonatal Outcomes[a*]	Unicornuate uterus	No unicornuate uterus	Crude OR (95% CI)	Adjusted OR (95% CI)	Adjusted p-value
SGA	89 (11.1)	100,106 (2.6)	4.73 (3.79 – 5.89)	4.90 (3.87 - 6.21)	<0.0001
IUFD	1 (0.1)	15,401 (0.4)	0.30 (0.04 - 2.11)	0.38 (0.05 - 2.69)	0.33

SGA, small for gestational age; IUFD, intrauterine fetal demise

a- Neonatal outcomes were adjusted for age, race, medical insurance plan type, income quartiles, obesity, previous Caesarian section, chronic hypertension, thyroid disease, IVF, hypertensive disorders of pregnancy, gestational hypertension, preeclampsia, preeclampsia/eclampsia superimposed hypertension and gestational diabetes

Discussion

To date, limited literature exists to guide optimal obstetrical surveillance and management of patients diagnosed with unicornuate uterus. The present study aims to provide an analysis of a population database to provide evidence-based insight on fertility, and pregnancy, maternal and neonatal outcomes associated with patients with unicornuate uterus.

In Figure 1, the prevalence of unicornuate uterus appears to have increased significantly from 2010 and has remained stable after 2011. This apparent increase may be explained by the introduction of the unicornuate code in 2010 and the inclusion in subsequent years as more health care providers became aware of the code and they started to bill for the anomaly. Hence, we performed another prevalence analysis from 2011 to 2014, and it was not statistically significant ($p = 0.45$).

Women with a unicornuate uterus have been reported to have poor reproductive outcomes such as infertility, subfertility and associated morbidities.[11] Though incompletely understood, causative factors for impaired fertility and adverse obstetrical outcomes in patients with unicornuate uterus have been attributed to cervical incompetence, lack of adequate uterine muscle, reduced uterine vasculature, or a restricted uterine length that hinders fetal development.[4] While spontaneous conception in women with a unicornuate uterus is possible, this anomaly is more commonly found in infertile women.[12] With the advent of IVF, women with a unicornuate uterus with adequate uterine cavity have been able to achieve higher conception rates.[15] However, regardless of the method of conception, women with unicornuate uterus remain a high-risk obstetrical group.[16]

Previous studies have reported rates for live birth of 29.2%, miscarriage of 29%, and premature birth of 44% (Akar et al. 2005). While insightful, these previous estimates vary quite significantly across available studies, largely a result of limited sample sizes. Intensive monitoring throughout pregnancy thus remains essential given that current interventions such as metroplasty of unicornuate uterus prior to pregnancy, or prophylactic cervical cerclage prior to or during pregnancy, are of uncertain benefit in enhancing reproductive outcomes.[13,16]

Moreover, in our study, women with such unicornuate anomaly were shown to be more likely to have utilized assisted reproductive technologies such as IVF. Indeed, one study evaluated clinical outcomes following IVF-intracytoplasmic sperm injection (ICSI) treatment in unicornuate uteri and demonstrated that these patients had lower clinical pregnancies and live birth rates relative to controls.[12] Additionally, it was suggested that blastocyst culture may further improve treatment outcomes; nonetheless, further studies are indicated to corroborate these findings.[12]

In the present study, women with a unicornuate uterus were shown to be at a higher risk of developing chronic hypertension and pre-gestational thyroid disease. Given that women at baseline are at greater risk of developing thyroid disease, thyroid dysfunction can independently exacerbate adverse reproductive and pregnancy outcomes[17,18] given the increased risk of miscarriage, placental abruption and growth restriction.[19] Thus, it remains critical to screen patients with known uterine anomalies for thyroid dysfunction prior to and during early pregnancy to mitigate the risk of adverse maternal and fetal outcomes.

Patients with unicornuate uterus were also shown to have an increased risk of hypertensive disorders of pregnancy and gestational diabetes mellitus (GDM). Increased prevalence of thyroid dysfunction amongst women with a unicornuate uterus, as demonstrated in the present study, has been suggested as a risk-factor for gestational diabetes mellitus; thus, thyroid dysfunction may influence the greater

incidence of GDM in this population.[20] As a result, and in accordance with the American Thyroid Association,[19] it remains imperative to continue to implement proper screening for women with known uterine anomalies in order to optimize medical management of thyroid dysfunction prior to, and/or during pregnancy. Indeed, screening and treatment of thyroid dysfunction are practiced to lower the risk of many adverse obstetrical outcomes such as GDM, caesarean delivery, preeclampsia, and stunted fetal development, among others.[19]

Finally, prevalence of preeclampsia appeared to be greater in the unicornuate group relative to the controls, consistent with previous studies, in which 71% patients with unicornuate uteri were reported to have mild preeclampsia alongside proteinuria.[21] As a result of the sub-optimal uterine environment associated with a unicornuate uterus, functional modifications to the uterus may affect the invasion of spiral arteries by cytotrophoblast cells, potentially culminating in this complication.[22] Given that preeclampsia imposes a risk to both mother and fetus, it is critical to take several preventative approaches for high-risk patients such as those with uterine anomalies.[23] It is suggested that low molecular weight heparin, enoxaparin, and micronutrients such as vitamin D, calcium and folic acid can help prevent preeclampsia. Thus, this cost-effective regimen may be introduced to at-risk patients, such as those with a unicornuate uterus.[23] Severity of preeclampsia was not specified within the present database; thus, future studies should aim to evaluate the indications and efficacy of available management strategies of preeclampsia within this patient population.

With regards to delivery outcomes, the present study demonstrated that individuals with a unicornuate uterus have a higher incidence of adverse obstetrical outcomes including PPROM, in line with previous studies.[16,24,25] Risk factors for PPROM include high BMI, GDM and cervico-isthmic abnormalities, which may cause cervical incompetence, all of which have been shown to be associated with congenital uterine anomalies including unicornuate uterus.[26] PPROM is responsible for 40% of all spontaneous preterm births,[26] consistent with our findings relating to the rates of premature delivery being significantly higher within the unicornuate group relative to controls. Preterm delivery may also be a result of a small asymmetrical uterine volume/cavity and/or reduced blood flow resulting from a lack or distorted uterine or ovarian artery or cervical incompetence, all of which may place increased pressure on the uterus thus increasing the risk of premature delivery.[27,28]

Our study also found that operative vaginal delivery was more prevalent within the control group while, caesarean delivery was significantly more common within the unicornuate group (84.5%), relative to controls (32.3%, $p<0.0001$). Given that this uterine anomaly is associated with adverse pregnancy and delivery outcomes and/or fetal malpresentation, elective caesarean delivery may be warranted to minimize maternal and/or fetal morbidity and mortality.[16]

Children born to mothers in the unicornuate group had an increased incidence of SGA ($p<0.0001$), likely, due to the smaller, sub-optimal uterine environment hindering fetal growth.[28] The lack of proper development of functional vessels within a unicornuate uterus may cause intrauterine fetal growth restriction or intrauterine fetal death as a result of placental insufficiency and oxidative stress.[22] These findings are further corroborated by a previous study which reported prevalence of SGA as 12.3% within the Mullerian anomaly group versus 6.8% in controls.[25] Through proper testing and screening, high-risk pregnancies can be identified with this uterine anomaly, and adverse complications such as those described within this study can be monitored to help limit intrauterine fetal growth restriction and thus reduce the risk of having an SGA neonate.

Limitations

The present study is not without its limitations. A large administrative database over a four-year period from 2010 to 2004 was utilized in this study. This presents as a limitation given the lack of recent data, though, the number deliveries that took place within the study period are of substantial statistical power. Given that the database utilized a code to differentiate women with and without a unicornuate uterus, it remains a possibility that undiagnosed unicornuate women were grouped in the control. Specifically, women that did not have any fertility issues and/or adverse obstetric or reproductive outcomes. Moreover, the inability to categorize and differentiate the different types of unicornuate uteri remains a critical limitation of the HCUP-NIS database. Though the study's sample size of women with a unicornuate uterus is large, the primary data utilized within this study, is based off coding from the administrative database which is prone to high-risk selection bias. Given the lack of knowledge regarding diagnostic tools, it remains imperative to recognize that quality, reliability, and validity of diagnosis may be low. Furthermore, the database did not provide any information regarding medications that the mothers had taken prior to and/or during pregnancy in order to evaluate degree and appropriateness of management of associated conditions and complications relating to this uterine anomaly. Similarly, it also remains unclear whether medications used had an independent negative impact on maternal and neonatal outcomes. Finally, it remains unclear if the patients had received previous treatment for their unicornuate uterus, such as prophylactic cervical cerclage, or had any interventions during pregnancy, which may also pose a significant impact on outcomes examined.

However, to our knowledge, this is the first study of its kind to provide a detailed analysis with substantial statistical power and over 3 million deliveries, in order to provide clinical guidance for optimal surveillance and management of these women.

Conclusion

Women with unicornuate uterus are at higher risk for adverse reproductive outcomes and may benefit from increased surveillance to prevent and/or decrease maternal and neonate morbidity and mortality.

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Conflicts of interest

The authors did not report any potential conflicts of interest.

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