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Reproductive outcome in 326 women with unicornuate uterus

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KEYWORDS: adenomyosis; ectopic pregnancy; endometriosis; miscarriage; uterine anomaly

CONTRIBUTION

What are the novel findings of this work?
We found that a unicornuate uterus is associated with a lower live-birth rate and a higher risk of ectopic pregnancy, miscarriage, preterm delivery and malpresentation at birth in comparison to pregnancies in which the uterus is normally formed. Women with a unicornuate uterus were more likely to have adenomyosis and endometriosis, the risk of the latter being greatest in those with a functional rudimentary horn.

What are the clinical implications of this work?
These findings should inform the counseling of women with a unicornuate uterus. Removal of a functional rudimentary horn to prevent ectopic pregnancy should be discussed with the patient. Pregnant women with a unicornuate uterus have a higher risk of adverse outcome and warrant close monitoring.

ABSTRACT

Objectives *To study the reproductive outcomes of women with a unicornuate uterus and compare them to those of women with no congenital uterine anomaly.*

Methods *This was a single-center, retrospective cohort study. Cases were women aged at least 16 years who were diagnosed with a unicornuate uterus on transvaginal/transrectal ultrasound between January 2008 and September 2021. Controls were women with no congenital uterine anomaly matched 1:1 by age and body mass index. The primary outcome was live-birth rate. Secondary outcomes were pregnancy loss (miscarriage, ectopic pregnancy, termination of pregnancy), preterm delivery, mode of delivery and concomitant gynecological abnormalities (endometriosis, adenomyosis, fibroids).*

Results *Included in the study were 326 cases and 326 controls. Women with a unicornuate uterus had a significantly lower live-birth rate (184/388 (47.4%)* vs *229/396 (57.8%);* $P = 0.004$*) and higher rates of overall miscarriage (178/424 (42.0%)* vs *155/465 (33.3%); adjusted odds ratio (aOR), 2.21 (95% CI, 1.42–3.42),* $P < 0.001$*), ectopic pregnancy (26/424 (6.1%)* vs *11/465 (2.4%); aOR, 2.52 (95% CI, 1.22–5.22),* $P = 0.01$*), preterm delivery (45/184 (24.5%)* vs *17/229 (7.4%); aOR, 3.04 (95% CI, 1.52–5.97),* $P = 0.001$*) and Cesarean delivery (116/184 (63.0%)* vs *70/229 (30.6%); aOR, 2.54 (95% CI, 1.67–3.88),* $P < 0.001$*). Rudimentary-horn pregnancies accounted for 7/26 (26.9%) ectopic pregnancies in the study group. Women with a unicornuate uterus were more likely to have endometriosis (17.5%* vs *10.7%;* $P = 0.018$*) and adenomyosis (26.7%* vs *15.6%;* $P = 0.001$*), but were not more likely to have fibroids compared with controls. Women with a functional rudimentary horn were more likely to have pelvic endometriosis compared to those without (odds ratio, 2.4 (95% CI, 1.4–4.1),* $P = 0.002$*).*

Conclusions *Pregnant women with a unicornuate uterus should be classified as high risk. Removal of a functional rudimentary horn should be discussed with the patient to prevent a rudimentary-horn ectopic pregnancy.* © *2022 The Authors. Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

The unicornuate uterus is a relatively rare type of congenital uterine anomaly that is present in approximately 1 in 500 women, accounting for 4–10% of all major uterine

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anomalies[1–3]. It results from complete or partial failure of the development of one of the Müllerian ducts[1,4]. Concomitant urinary tract abnormalities have been reported in up to 40% of cases, of which the most common is unilateral renal agenesis[5]. The prevalence of a unicornuate uterus is reported to be higher in women with a history of infertility and recurrent miscarriage[4,6]. However, the real impact of this anomaly on reproductive outcome is still unclear as, historically, it was diagnosed only in highly selective patient groups, such as women presenting with infertility, pelvic pain or rudimentary-horn pregnancy[7,8]. Furthermore, most published studies include small numbers of women in whom the diagnosis of a uterine anomaly was made during surgery or on hysterosalpingography, which are prone to confirmation bias[3,9–12].

With the advent of high-resolution diagnostic ultrasound, a unicornuate uterus can be diagnosed non-invasively on two-dimensional (2D) B-mode transvaginal ultrasound (TVS) by demonstrating a single interstitial tube at the uterine fundus[13]. Three-dimensional (3D) ultrasound offers superior views of uterine anatomy to 2D imaging, and has been generally accepted as the optimal modality for the diagnosis of Müllerian anomalies, including the unicornuate uterus[2,14–17].

The clinical presentation of women with a unicornuate uterus is variable owing to the heterogeneity of the four morphological variants. It has been reported previously that in most cases, there is a functional, non-communicating rudimentary horn[13,18]. Severe dysmenorrhea and pregnancy and obstetric complications are common in women with this condition[18], and they are also at risk of developing chronic pelvic pain and endometriosis at a young age[19–21].

The primary aim of this study was to evaluate reproductive outcome in a large group of women with a unicornuate uterus who were attending our general gynecology clinic. We also studied the frequency of different subtypes of unicornuate uterus and their association with urogenital abnormalities and acquired benign gynecological conditions.

METHODS

This was a single-center, retrospective cohort study of consecutive women presenting with a unicornuate uterus and a control group with a normally shaped uterus who attended the Gynecology Diagnostic and Outpatient Treatment Unit at University College London Hospital (UCLH) between January 2008 and September 2021. Ethics approval was waived by the National Health Service Research Ethics Committee and the Joint Research Office at UCLH, as the data had already been collected as part of routine care, were anonymized and were analyzed within the care team.

Study population

The study group included all women aged 16 or over who attended our clinic, regardless of indication, and were diagnosed with a unicornuate uterus. This included women attending for an early pregnancy check-up. We excluded women who were unable to undergo TVS or transrectal ultrasound (TRS) (unless they had pelvic magnetic resonance imaging), those who had had a hysterectomy, or if they had uterine fibroids that precluded satisfactory visualization of the uterine cavity, preventing exclusion of a uterine anomaly. Demographic data, clinical, gynecological, obstetric and surgical history and indications for the first ultrasound examination were obtained from the electronic clinical database (Viewpoint version 5.6 (Bildverarbeitung GmbH, Munich, Germany) and Epic Live (Epic System Corporation, Verona, WI, USA)), in which this information is stored routinely.

The controls were women with a normally shaped uterus as determined by one of two experienced examiners, attending the same clinic for a variety of indications. They were matched by age (±1.0 year) and body mass index (±2 kg/m^2) at inclusion, using the SPSS-case–control matching function (SPSS Statistics version 22.0 (IBM Corp., Armonk, NY, USA)). Ultrasound images and clinical data pertaining to the control group were collected prospectively under the scope of different studies, of which one has been published[22].

Image acquisition

All women were examined with either TVS or TRS, using a 4–9-MHz probe with 3D facility (Voluson E8; GE Healthcare, Zipf, Austria). Ultrasound examinations were carried out systematically in all patients. A dynamic 2D-TVS assessment was performed first to assess the position and morphological appearance of the pelvic organs (uterus, cervix, ovaries and adnexal regions, bladder, distal portion of the ureters, rectosigmoid colon). The examination of the uterus included performing a series of parallel transverse sections from the cervix to the fundus, until the interstitial portions of the Fallopian tubes were visualized. Following that, a right-to-left sweep was carried out in the longitudinal plane, facilitating visualization of the endometrium and measurement of its thickness. 3D-TVS volumes of the uterus were also acquired in all women. Analysis of uterine morphology was performed in a standardized coronal reconstructed plane using the interstitial portions of the Fallopian tubes as reference points. The examination technique has been described previously[14] and allows confirmation of the diagnosis of a unicornuate uterus with greater precision than does 2D-TVS alone. A diagnosis was made upon demonstrating a uterine cavity that narrowed rather than widened in the fundal area and continued into a single interstitial portion of Fallopian tube (Figures 1 and 2).

The rudimentary horn was typically seen as a small, solid, round structure located between the unicornuate uterus and the contralateral ovary. It appeared hypoechogenic on ultrasound, resembling the myometrium of the unicornuate uterus. A functional cavity within the rudimentary horn (i.e. a functional rudimentary horn) was identified by direct visualization of a hyperechogenic

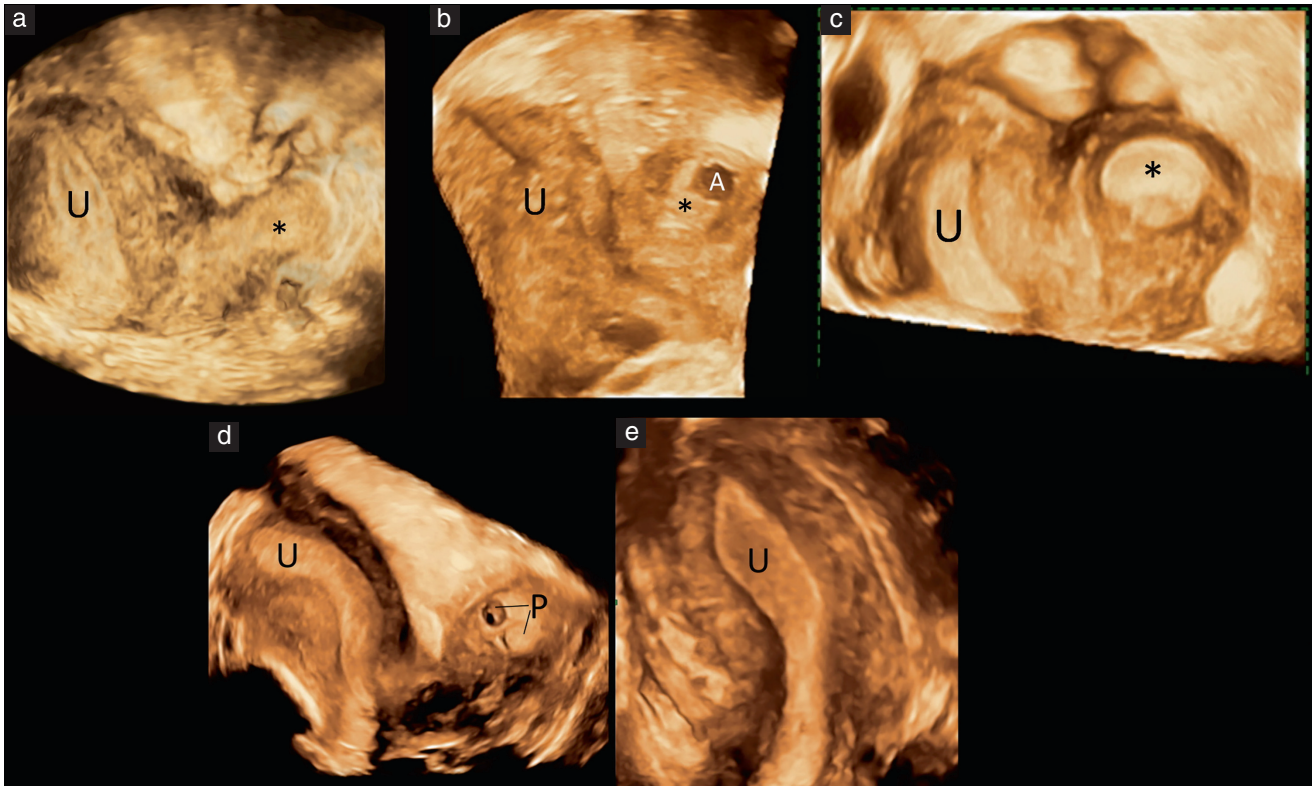

Figure 1 Three-dimensional transvaginal ultrasound rendering of unicornuate uterus in coronal plane in four patients, showing hemiuterus (U) and rudimentary horn (*). (a) Right hemiuterus and non-functional left rudimentary horn. Cavity of hemiuterus is narrow in fundal area and only a single interstitial portion of Fallopian tube is visible. (b) Right hemiuterus and non-communicating left rudimentary horn. Cavity of horn contains functional endometrium with visible adenomyosis (A), represented by anechoic myometrial cyst with thin hyperechogenic rim protruding into cavity. (c) Right hemiuterus with hyperechogenic endometrium and functional, non-communicating left rudimentary horn, with blood distending the cavity. (d) Right hemiuterus and duplex ectopic pregnancy in non-communicating left rudimentary horn, where two gestational sacs (P) are visualized. (e) Right hemiuterus in same woman as in (d), 3 months after uneventful excision of rudimentary horn containing ectopic pregnancy.

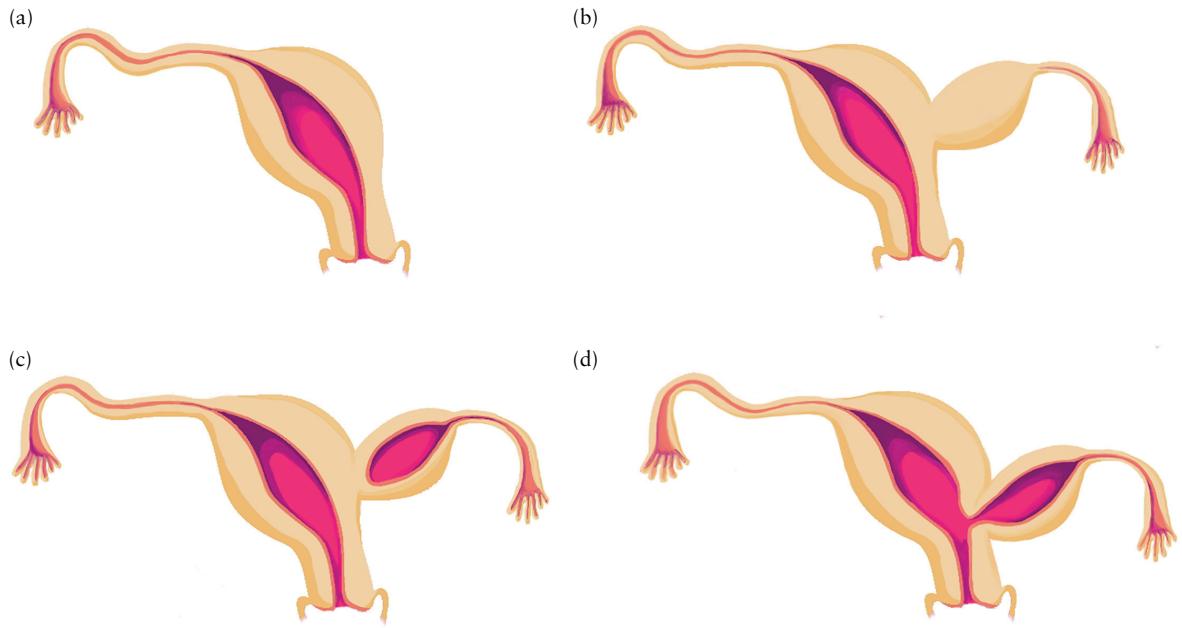

Figure 2 Schematic diagram depicting subtypes of unicornuate uterus: (a) hemiuterus without rudimentary horn; (b) hemiuterus with non-functional rudimentary horn; (c) hemiuterus with functional, non-communicating rudimentary horn; and (d) hemiuterus with functional, communicating rudimentary horn.

endometrium (Figure 1c,d)[13,14]. We categorized the congenital uterine anomalies according to the American Society for Reproductive Medicine classification (Figure 2)[23]. All pregnant women with suspected uterine anomalies were invited for follow-up scans after delivery to confirm the diagnosis. Transabdominal ultrasound was performed to assess the kidneys whenever a unicornuate uterus was found.

Any concomitant pelvic abnormalities diagnosed on ultrasound were recorded. The diagnosis of acquired uterine abnormalities was made by direct ultrasonographic visualization. Adenomyosis was diagnosed when one or more direct signs or several indirect signs, as described by the Morphological Uterus Sonographic Assessment group, were seen[24,25]. Direct signs included anechoic myometrial cysts, hyperechogenic foci and islets and echogenic subendometrial lines and buds invading the junctional zone; indirect signs included a globular uterus, asymmetrical thickening of the uterine walls, fan-shaped shadowing and irregular widening of the junctional zone. Color Doppler was used to discriminate adenomyotic myometrial cysts from uterine blood vessels to avoid false-positive diagnoses[24–27]. Diagnostic criteria for fibroids were the appearance of well defined lesions within or connected to the myometrium of the uterine corpus or the cervix with posterior shadowing and circumferential vascularity[25,28]. Endometriosis was diagnosed as per the consensus statement formulated by the International Deep Endometriosis Analysis group[29,30]. Endometriotic nodules were defined as hypoechogenic, avascular, solid lesions with irregular outer margins, found in various locations including the abdominal wall, adnexa, bladder, bowel, pouch of Douglas, rectovaginal space and septum, uterosacral ligaments, uterovesical fold and vagina. Endometriomas were characterized as well-defined, thick-walled, avascular ovarian lesions displaying ground-glass echogenicity.

All images were stored electronically in our clinical database together with the women's demographic, clinical and ultrasound data (Viewpoint version 5.6). The primary examination was performed by clinical fellows with ultrasound expertise corresponding to the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) Level II. All diagnoses (including acquired abnormalities) were confirmed by specialist gynecologists with more than 10 years of experience, corresponding to EFSUMB Level III.

Study outcomes

The primary outcome of the study was the live-birth rate, defined as the proportion of live births from all pregnancies, not including terminations of pregnancy. Live birth was defined as the delivery of a fetus that showed evidence of life after 22 weeks' gestation. Secondary outcomes were the rates of pregnancy loss, grouped by early (before 15 weeks' gestation) and late ($15+1$ to $22+6$ weeks' gestation) miscarriage and ectopic pregnancy (stratified by location as defined by the European Society of Human Reproduction and Embryology[31]), as well as the proportion of women who suffered recurrent miscarriage (defined as a history of three or more miscarriages at or before $14+6$ weeks' gestation, as the order in which they occurred in relation to the live birth could not be determined retrospectively). Further secondary outcomes were preterm delivery (defined as delivery between $23+0$ and $36+6$ weeks' gestation) and mode of delivery (Cesarean section or vaginal delivery). We also analyzed the proportions of women diagnosed with endometriosis, adenomyosis, uterine fibroids and genitourinary and anorectal tract abnormalities.

Statistical analysis

Statistical analysis was performed using SPSS Statistics version 22.0 (IBM Corp.). The distribution of data was assessed using the Kolmogorov–Smirnov test. Descriptive statistics are presented as mean ± SD for normally distributed data, median (range) for non-normally distributed data and *n* (%) for categorical data. Differences in means between groups were analyzed using Student's *t*-test and distributions of non-parametric data were compared with the Mann–Whitney *U*-test. The χ-square test, Fisher's exact test or the Fisher–Freeman–Halton exact test were used to compare categorical variables and proportions; $P < 0.05$ was considered to indicate statistical significance. Binary logistic regression analysis was performed to calculate the odds ratio (OR) for adverse outcomes, adjusting for potentially confounding effects that were available in our data and reported in previous studies. Only one confounding variable was included when two possible confounders showed a high correlation (for example, endometriosis and adenomyosis) to avoid overestimating the effect. The confounder described previously as most relevant for the outcome, i.e. endometriosis for infertility and adenomyosis for miscarriage, was selected.

We performed a *post-hoc* power analysis with the obtained sample size and the results of the primary outcome (live-birth rate), which resulted in a power of 80.4% at an alpha level of 0.05.

RESULTS

Population characteristics

During the study period, 340 women presented with a suspected unicornuate uterus, of whom 326 were included in the final analysis in addition to 326 matched controls, resulting in a study population of 652 patients. The study flowchart is presented in Figure 3. Demographic data are shown in Table 1, and primary indications for the first visit are presented in Table 2. Forty-six patients with a unicornuate uterus attended the unit for early pregnancy complications such as vaginal bleeding or pain, of whom 26 (56.5%) had a known unicornuate uterus and 20 (43.5%) were newly diagnosed at this visit and confirmed after delivery. Among women with a unicornuate uterus, 177/326 (54.3%) were diagnosed with the uterine anomaly at their initial visit, while the

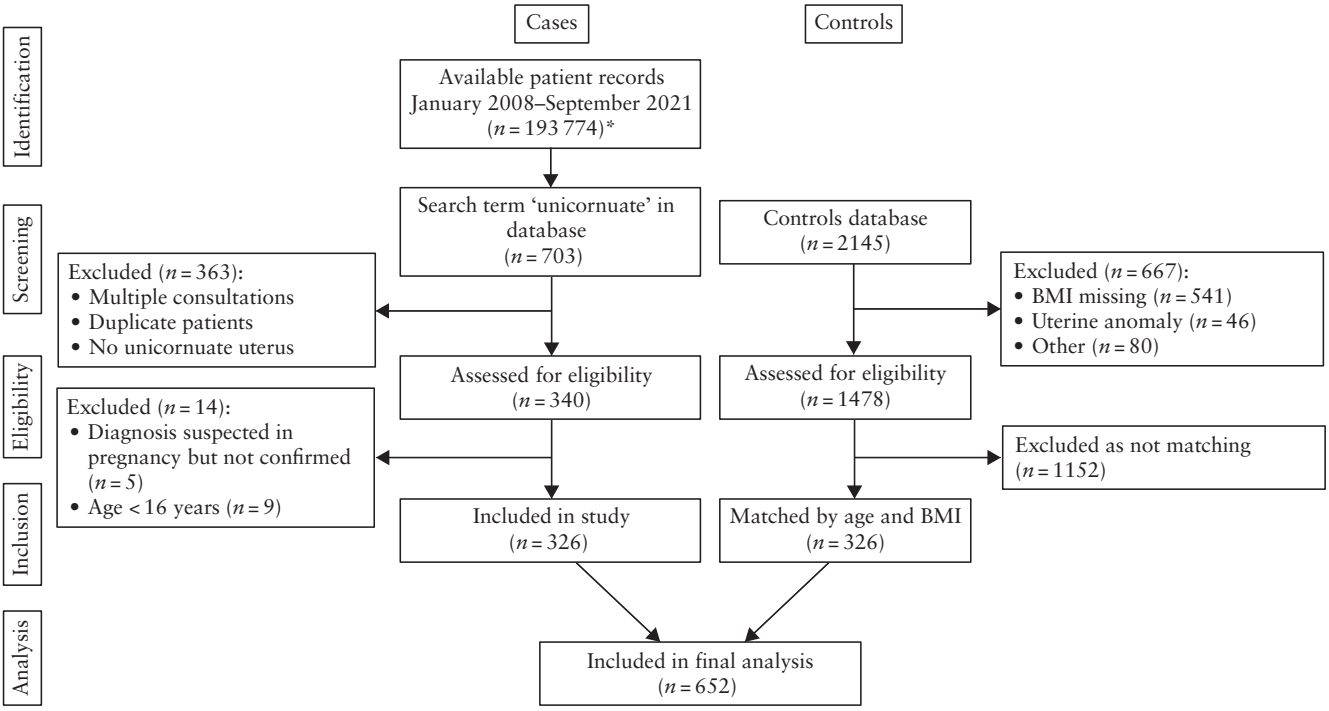

Figure 3 Flowchart summarizing inclusion of patients in study. *Representing clinical consultations, not individuals. BMI, body mass index.

Table 1 Demographic and clinical characteristics of 326 women with unicornuate uterus and 326 controls matched for age and body mass index (BMI)

Characteristic	*Unicornuate uterus* (n = *326*)	*Controls* (n = *326*)	P
Age (years)	34.0 ± 9.5	34.2 ± 9.6	
BMI (kg/m^2)	22.0 (17.4–35)	22.0 (16–36)	
Ethnicity			
Caucasian	249 (76.4)	235 (72.1)	
Afro-Caribbean	21 (6.4)	25 (7.7)	
Middle Eastern	15 (4.6)	9 (2.8)	
Asian	21 (6.4)	42 (12.9)	
Mixed/other	12 (3.7)	15 (4.6)	
Not reported	8 (2.5)	0 (0)	
Gravidity	1 (0–10)	1 (0–15)	0.566*
Parity	0 (0–5)	0 (0–13)	0.291*
Previous surgery for endometriosis	31 (9.5)	28 (8.6)	0.682†
Previous myomectomy	7 (2.1)	13 (4.0)	0.173†
Previous cone biopsy	10 (3.1)	22 (6.7)	0.03†

Data are given as mean ± SD, median (range) or *n* (%). *Mann–Whitney *U*-test. †Pearson's chi-square test.

Table 2 Primary indication for first clinic visit in 326 women with unicornuate uterus and 326 matched controls

Primary indication	*Unicornuate uterus* (n = *326*)	*Controls* (n = *326*)
Pelvic pain including dysmenorrhea	83 (25.5)	99 (30.4)
Abnormal uterine bleeding	59 (18.1)	84 (25.8)
Infertility	50 (15.3)	14 (4.3)
Early-pregnancy complications	46 (14.1)	83 (25.5)
Suspected uterine anomaly	45 (13.8)	0 (0)
Ovarian abnormalities	21 (6.4)	32 (9.8)
Other	22 (6.7)	14 (4.3)

Data are given as *n* (%).

remainder had been diagnosed previously or were referred to confirm a suspected diagnosis. A suspected unicornuate uterus was the reason for referral to our unit in 45/326 (13.8%) cases.

There was a similar number of left and right hemiuteri (153/326 (46.9% (95% CI, 41.4–52.5%)) *vs* 173/326 (53.1% (95% CI, 47.5–58.6%)); $P = 0.26$). The rates of late and early miscarriage, having at least one miscarriage and preterm delivery were not significantly different between women with a left hemiuterus and those with a right hemiuterus (all $P > 0.39$). A rudimentary horn was observed in 218/326 (66.9%) women with a unicornuate uterus, with non-functional horns being more common than the functional type (57.8% *vs* 42.2%) (Table 3). Laparoscopic excision of the rudimentary horn was performed in 52/218 (23.9%) women with a rudimentary horn, of which the majority (47/52 (90.4%)) had functional horns.

Concomitant congenital urogenital anomalies

A detailed list of concomitant congenital anomalies according to the type of unicornuate uterus is shown in Table 3. We found a total of 88 vaginal, renal/urinary tract or cloacal abnormalities in 68/326 (20.1%) women with a unicornuate uterus compared with just a single case (0.3%) of epispadia in the control group ($\chi^2 = 72.76$; $P < 0.001$). Renal agenesis contralateral to the unicornuate uterus was the most common

Table 3 Concomitant congenital urogenital anomalies and acquired gynecological abnormalities in 326 women with unicornuate uterus, according to morphological subtype

	Rudimentary horn					
Anomaly	*Absent* (n = *108*)	*Non-communicating non-functional* (n = *126*)	*Non-communicating functional* (n = *88*)	*Communicating functional* (n = *4*)	n	P*
Concomitant urogenital malformation						
Renal agenesis	16 (14.8)	5 (4.0)	17 (19.3)	1 (25.0)	39	0.003
Pelvic kidney	10 (9.3)	1 (0.8)	0 (0)	0 (0)	11	0.001
Other urinary tract malformation	8 (7.4)	3 (2.4)	6 (6.8)	1 (25.0)	18	0.097
Vaginal malformation	5 (4.6)	2 (1.6)	6 (6.8)	1 (25.0)	14	0.05
Genetic syndrome	7 (6.5)	0 (0)	2 (2.3)	0 (0)	9	0.025
Cloacal anomaly	3 (2.8)	1 (0.8)	2 (2.3)	0 (0)	6	0.693
Concomitant gynecological abnormality						
Endometriosis	17 (15.7)	17 (13.5)	23 (26.1)	0 (0)	57	0.071
Adenomyosis	27 (25.0)	36 (28.6)	24 (27.3)	0 (0)	87	0.603
Fibroids	15 (13.9)	22 (17.5)	15 (17.0)	1 (25.0)	53	0.839
Surgery for endometriosis	8 (7.4)	8 (6.3)	15 (17.0)	0 (0)	31	0.041
Excision of rudimentary horn	—	5 (4.0)	46 (52.3)	1 (25.0)	52	
Before first pregnancy	—	5 (4.0)	36 (40.9)	0 (0)	41	

Data are given as *n* (%) or *n*. *Fisher–Freeman–Halton exact test.

abnormality, occurring in 39 (12.0%) women, followed by pelvic kidney, which was found in 11 (3.4%) women, almost all of whom lacked a rudimentary horn ($P = 0.02$).

Reproductive outcome

There were similar proportions of gravidas in the study and control groups. The total number of pregnancies and median number of pregnancies per gravid woman were also similar (Table 4). However, the proportion of pregnancies lost through miscarriage was significantly higher in women with a unicornuate uterus than in the control group, resulting in a significantly lower live-birth rate (184/388 (47.4% (95% CI, 42.4–52.5%)) *vs* 229/396 (57.8% (95% CI, 52.8–62.7%)); $P = 0.004$). While the rate of early miscarriage was higher in the study group, this difference did not reach statistical significance (Table 4). However, among gravid women, the proportion of those experiencing at least one early miscarriage was significantly higher in the unicornuate-uterus group (98/173 (56.6% (95% CI, 49.2–63.9%)) *vs* 75/180 (41.7% (95% CI, 34.6–49.1%)); $P = 0.005$), and the adjusted odds ratio (aOR) for having at least one early or late miscarriage was also significantly higher in the study group. There were no significant differences in the proportions of women in the study and control groups who experienced recurrent pregnancy loss. Among women with previous pregnancies, there were more than twice as many ectopic pregnancies in the study group than in the control group (Table 4), and the aOR for having an ectopic pregnancy was more than double for women with a unicornuate uterus compared with those without.

The proportion of women who experienced preterm delivery before 37 weeks' gestation was three times higher in the study group than in the control group (Table 4). Regarding mode of delivery, women with a unicornuate uterus were significantly more likely to require delivery by Cesarean section, the main indication being malpresentation. The indications for Cesarean delivery are given in Table S1.

Concomitant acquired gynecological abnormalities

The frequency of endometriosis was significantly higher in women with a unicornuate uterus than in controls (57/326 (17.5%) *vs* 35/326 (10.7%); $P = 0.018$). Women with a functional rudimentary horn had the highest risk of developing endometriotic lesions (Table 3), with an OR of 1.96 (95% CI, 1.08–3.56) compared to women with a unicornuate uterus without a functional horn ($P = 0.025$). Compared to women without a functional horn, women with a functional horn had an increased risk of having endometriosis (OR, 2.4 (95% CI, 1.4–4.1); $P = 0.002$). Adenomyosis was also more common in women with a unicornuate uterus (87/326 (26.7%) *vs* 51/326 (15.6%); $P = 0.001$), but there was no difference in the frequency of fibroids between the two groups ($P = 0.059$). Moreover, there was no difference in the proportion of women in the study group with and without a functional horn who were diagnosed with adenomyosis (24/92 (26.1%) *vs* 63/234 (26.9%); $P = 0.878$) or fibroids (16/92 (17.4%) *vs* 37/234 (15.8%); $P = 0.740$) (Table 3). Among women with a functional rudimentary horn, those who underwent laparoscopic excision had a significantly lower prevalence of adenomyosis (8/47 (17.0%) *vs* 16/45 (35.6%); $P = 0.043$), but a similar prevalence of endometriosis (13/47 (27.7%) *vs* 10/45 (22.2%); $P = 0.55$), compared with those in whom the horn was not excised.

Reproductive outcome in women with and without functional rudimentary horn

We found no statistically significant difference in the total number of pregnancies or miscarriages or the miscarriage

Table 4 Reproductive outcome of 326 women with unicornuate uterus and 326 matched controls

Outcome	*Unicornuate uterus* (n = *326*)	*Controls* (n = *326*)	P	*OR (95% CI)*	P	*aOR (95% CI)*	P
Pregnancy outcome							
Gravidity ≥ 1	173 (53.1)	180 (55.3)	0.573‡				
Total pregnancies	424	465					
Pregnancies per gravida	2 (1–10)	2 (1–15)	0.859§				
Miscarriage	178/424 (42.0)	155/465 (33.3)	0.004‡	2.014 (1.32–3.08)	0.001	2.21 (1.42–3.42)¶	< 0.001
Early (< 15 weeks)	163/424 (38.4)	152/465 (32.7)	0.076‡	1.44 (1.01–2.04)	0.042	1.52 (1.06–2.19)¶	0.022
Late (15–22 weeks)	15/424 (3.5)	3/465 (0.7)	0.003‡	4.83 (1.38–16.97)	0.014	5.19 (1.47–18.33)**	0.01
Miscarriages per gravida	1 (0–7)	0 (0–10)	0.013§				
Early (< 15 weeks)	1 (0–6)	0 (0–10)	0.042§				
Late (15–22 weeks)	0 (0–2)	0 (0–1)	0.005§				
Recurrent pregnancy loss*	20 (11.6)	18 (10.0)	0.629‡				
Ectopic pregnancy	26/424 (6.1)	11/465 (2.4)	0.006‡	2.38 (1.15–4.92)	0.019	2.52 (1.22–5.22)††	0.013
Fallopian tube	17/26 (65.4)	11/11 (100)					
Rudimentary horn	7/26 (26.9)	0/11 (0)					
Cesarean scar	2/26 (7.7)	0/11 (0)					
Termination of pregnancy	36/424 (8.5)	69/465 (14.8)	0.004‡				
Obstetric outcome							
Live birth†	184/388 (47.4)	229/396 (57.8)	0.004‡				
Deliveries per gravida	1 (0–7)	1 (0–13)	0.306§				
PTD (23 to < 37 weeks)	45/184 (24.5)	17/229 (7.4)	0.003‡	2.62 (1.35–5.09)	0.004	3.04 (1.52–5.97)**	0.001
PTD per gravida	0 (0–3)	0 (0–4)	0.001§				
Cesarean section	116/184 (63.0)	70/229 (30.6)	< 0.001‡	2.36 (1.56–3.58)	< 0.001	2.54 (1.67–3.88)‡‡	< 0.001

Data are given as *n* (%), *n*, median (range) or *n*/*N* (%), unless stated otherwise. *Defined as ≥ 3 miscarriages. †No stillbirths were reported; denominator excludes termination of pregnancy. ‡Chi-square test. §Mann–Whitney *U*-test. ¶Adjusted for body mass index (BMI), adenomyosis and fibroids. **Adjusted for BMI and cone biopsy. ††Adjusted for endometriosis. ‡‡Adjusted for BMI. aOR, adjusted odds ratio; OR, odds ratio; PTD, preterm delivery.

Table 5 Reproductive outcome of 326 women with unicornuate uterus according to presence or absence of functional rudimentary horn

Outcome	*No functional horn* (n = *234*)	*Functional horn* (n = *92*)	P
Gravidity ≥ 1	131 (56.0)	42 (45.7)	0.094†
Total pregnancies	314	110	
Pregnancies per gravida	2 (1–8)	2 (1–10)	0.692*
Miscarriage	135/314 (43.0)	43/110 (39.1)	0.476†
Early (< 15 weeks)	125/314 (39.8)	38/110 (34.6)	0.335†
Late (15–22 weeks)	10/314 (3.2)	5/110 (4.6)	0.496†
Ectopic pregnancy	15/314 (4.8)	11/110 (10.0)	0.051†
Fallopian tube	14/15 (93.3)	3/11 (27.3)	
Rudimentary horn	0/15 (0)	7/11 (63.6)	
Cesarean scar	1/15 (6.7)	1/11 (9.1)	
Live birth	135/314 (43.0)	49/110 (44.5)	0.785†
Preterm delivery	33/133 (24.8)	12/49 (24.5)	0.967†
Cesarean section	82/133 (61.7)	34/49 (69.4)	0.339†

Data are given as *n* (%), *n*, median (range) or *n*/*N* (%). *Independent samples Mann–Whitney *U*-test. †Chi-square test.

rates between women with and those without a functional rudimentary horn (Table 5). Fifty-two women had their horn excised, of whom 21 (40.4%) had had at least one pregnancy. The proportion of women who had had at least one miscarriage did not differ significantly between those who had their horn excised before or after pregnancy (4/10 (40.0%) *vs* 5/11 (45.5%); $P = 0.801$).

The proportion of women with a functional rudimentary horn who reported a previous ectopic pregnancy was twice that of women without a functional horn (Table 5). This was mainly owing to the higher rate of ectopic pregnancies implanted within the rudimentary horn; the rate of tubal ectopic pregnancies was not significantly different (2.7% (3/110) *vs* 4.5% (14/314); $P = 0.41$).

Excluding women who underwent surgical excision of the rudimentary horn before the first pregnancy, 7/56 (12.5%) women with a functional rudimentary horn experienced a rudimentary-horn ectopic pregnancy, affecting 7/42 (16.7%) women who had had at least one pregnancy.

One woman was diagnosed with a rudimentary-horn pregnancy following horn rupture and fetal loss at 27 weeks' gestation. Another woman with a rudimentary-horn pregnancy was treated successfully with local methotrexate because of a significant surgical risk profile, while all other women underwent laparoscopic excision of the rudimentary horn. Of the 17 tubal ectopic pregnancies in the study group, eight were in women without a rudimentary horn and nine in women with a horn. Notably, only two of the latter were in the tube of the hemiuterus, while six were in the tube of the rudimentary horn and in one case the location was not reported. There was no difference in the frequency of preterm delivery or Cesarean section between those with and those without a functional horn (Table 5).

DISCUSSION

In this large cohort, we found that women with a unicornuate uterus at ultrasound assessment had a lower live-birth rate and were more likely to experience a range of adverse pregnancy outcomes than were women with a normally formed uterus.

Women with a unicornuate uterus were significantly more likely to experience miscarriage compared with controls, the difference being particularly large in the rate of second-trimester miscarriage. Furthermore, they had a higher risk for ectopic pregnancy and, as described previously, a higher risk for preterm delivery[4,32]. Previous studies have demonstrated inconclusive results regarding the risk of miscarriage. In their review, Reichman *et al.*[32] reported miscarriage rates in women with a unicornuate uterus of 24% for early losses and 10% for late losses, which differ from our findings. However, they had no control group, making it difficult to interpret their results. In another review, the reported risk for having an early miscarriage with a unicornuate uterus was significantly increased (risk ratio, 2.15 (95% CI, 1.3–4.5)), but the actual rates of miscarriage were not reported[4]. The risk of late miscarriage was not significantly increased, possibly owing to the small number of cases[4]. In addition to being published in case reports or case series, a significant proportion of women included in the studies in the review[4] were undergoing fertility treatment and invasive tests such as hysteroscopy or laparoscopy, which makes direct comparison with our data difficult[33,34]. Other studies reporting on pregnancy outcome in women with a unicornuate uterus were conducted in populations undergoing *in-vitro* fertilization, most of which do not compare their findings with controls[3,9,10,35,36].

In our study, the significantly higher rate of Cesarean delivery in women with a unicornuate uterus was due to malpresentation at delivery, with no increase in the rate of other fetal or maternal indications, which is in line with the data of a previous publication[37].

It has been hypothesized that late miscarriage and preterm birth occur in women with a unicornuate uterus owing to the inability of the relatively small unicornuate uterus to expand sufficiently to accommodate an advanced pregnancy. However, there is no obvious explanation for the high rate of early miscarriage. If impaired endometrial receptivity or abnormal uterine peristalsis were responsible, one would expect a reduction in the total number of pregnancies and a higher proportion of nulligravid women in those with a unicornuate uterus, which was not the case in our study.

Another important finding of this study was that having a unicornuate uterus increased significantly the risk of ectopic pregnancy of any type, with tubal ectopic pregnancies implanting preferentially in the tube of the rudimentary horn when present. Rudimentary-horn pregnancy is a rare event in the general population of women[38], therefore it may not be perceived as an important health problem[39]. However, we found that this potentially serious condition occurred in 17% of gravid women who did not have their functional horn removed prior to their first pregnancy. We did not find a significant difference in the frequency of other adverse pregnancy or obstetric outcomes between women with different subtypes of unicornuate uterus, which may be helpful when counseling these women[20,40,41].

A novel finding of our study was that adenomyosis was significantly more common in unicornuate uteri. The pathogenesis of adenomyosis could involve impaired uterine peristalsis within the abnormally shaped horn, with disruption of the junctional zone[42]. Another possible explanation is the presence of ectopic Müllerian remnants dislodged during embryogenesis[26,43]. We also found a higher prevalence of endometriosis in the study group, with the highest risk in women with a functional horn. These findings support the theory that retrograde menstruation contributes to the development of endometriosis in women with a unicornuate uterus.

In our study population, the unicornuate uterus was observed most commonly without a functional rudimentary horn. This finding is at odds with other studies that reported a predominance of functional non-communicating horns[11,44]. Functional horns are often symptomatic and are therefore more likely to be detected. Our ultrasound protocol required that both interstitial tubes were visualized in all women attending for ultrasound scans. This could explain the high detection rate of unicornuate uteri without a functional horn, which are less likely to present with symptoms suggestive of obstruction or retrograde menstruation.

Strengths and limitations

The main strengths of our study are that it reported on a large, consecutive cohort of women diagnosed with a unicornuate uterus, used highly sensitive, non-invasive diagnostic tests, provided detailed descriptions of uterine

morphology and included a control group. Our study is the first to analyze reproductive and gynecological outcomes with regard to the morphological subtype of the unicornuate uterus. Our diagnostic approach for detecting endometriosis and adenomyosis has been used in previous large-scale prospective studies and has been shown to be effective and accurate[26,30,45,46].

While all data for the control group were collected prospectively, the retrospective nature of the data collection for the study group presents an inherent limitation. Detailed information about the symptoms that led to the diagnosis of unicornuate uterus, age at diagnosis, if prematurity was iatrogenic, history of infertility and indication for rudimentary-horn excision, as well as histological confirmation of excised horns following surgery in other hospitals, was not available in all cases. Also, the women's age at the time of each pregnancy could not be determined accurately.

However, data on the number of pregnancies and miscarriages were usually reported and recorded with high accuracy and are therefore reliable. This condition, combined with the relatively large study sample, strengthens our assumption that the retrospective nature of our study did not significantly affect our conclusions regarding pregnancy outcome.

Another limitation is that the study and control groups may not have been representative of the general population, as this was a cohort of women attending a general gynecology service presenting with various clinical symptoms. This selection bias is reflected in the high miscarriage rate in the control group. Women with a unicornuate uterus that experienced no gynecological problems and did not undergo examination are missing from our study population. However, many women attended the clinic for symptoms potentially unrelated to uterine malformation, such as postmenopausal bleeding or ovarian pathology, so we still believe our cases are broadly representative. As some women with fibroids were excluded owing to an inability to make a conclusive diagnosis or exclude a uterine anomaly, the true prevalence of fibroids in the study and control groups may differ from our reported numbers.

Conclusions and recommendations

This study has shown that a unicornuate uterus is associated with an increased risk of adverse pregnancy outcome. In view of that, a detailed systematic examination of uterine morphology should be carried out in routine clinical practice to detect unicornuate uteri. Women with a unicornuate uterus and a functional rudimentary horn are at particularly high risk of both pelvic endometriosis and rudimentary-horn pregnancy. Laparoscopic excision of the rudimentary horn to prevent potentially serious complications should be discussed with the patient. The risk of tubal ectopic pregnancies is increased in all women with a unicornuate uterus, and ultrasound scans should be arranged in early pregnancy to facilitate their detection before tubal rupture has a chance to occur.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Indications for Cesarean delivery in 116 women with unicornuate uterus and 70 controls