A Retrospective Analysis of Female Müllerian Duct Anomalies in Association With Congenital Renal Abnormalities

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A B S T R A C T

Study objective: Müllerian (paramesonephric) duct anomalies (MDAs) are associated with several coexisting congenital abnormalities, including renal abnormalities. Although congenital renal abnormalities may remain asymptomatic, the consequences should not be underestimated. In both the literature and clinical practice, it remains necessary to improve awareness of the co-occurrence of different congenital renal abnormalities in women with MDAs. To gain further insight into this co-occurrence and to estimate whether guidelines for women with MDAs should be optimized, this study was performed.
Design: A descriptive retrospective analysis.
Setting: University Medical Centre Utrecht in the Netherlands.
Participants: Women with MDAs diagnosed or treated between 1980 and 2015.
Interventions: None.
Main outcome measures: The prevalence of the co-occurrence of congenital renal abnormalities in women with MDAs.
Results: Renal status was recorded in 186 of 255 women (72.9%), and the other women (27.1%) did not have a retrievable renal status. Congenital renal abnormalities were present in 90 of 186 women (48.4%) and were observed most frequently in women having a duplex uterus with obstructed hemivagina. The most common renal abnormality was unilateral renal agenesis, which was observed in 58 of 90 women (64.4%).
Conclusions: MDAs are highly associated with different congenital renal abnormalities, and these results emphasize that women with MDAs should be routinely screened for their co-occurrence. However, these results also highlight that there remains a lack of awareness of this association. Whether all women with congenital renal abnormalities should be routinely screened for MDAs requires further investigation.
Key Words: Müllerian ducts, Urogenital system, Urogenital abnormalities

Introduction

Müllerian (paramesonephric) duct anomalies (MDAs) are the result of partial or complete failure of embryonic development of the Müllerian ducts and their derivatives,[1] including the fallopian tubes, uterus, cervix, and proximal part of the vagina. The distal part of the vagina derives from the urogenital sinus.[2] A well-known MDA is complete vagina and uterine agenesis, often referred to as the eponym Mayer–Rokitansky–Kuster–Hauser (MRKH) syndrome.[3] However, a wide range of phenotypic manifestations of MDAs have been described. Furthermore, several coexisting congenital abnormalities are associated with MDAs. These abnormalities include mainly congenital renal abnormalities, but ovarian, skeletal, auditory, cardiac, and gastrointestinal abnormalities have also been reported.[4-14] The association with urological abnormalities, for MRKH syndrome in particular, was described as early as 1910.[15] The co-occurrence of congenital renal abnormalities can be explained by the fact that both the genital and urinary tracts are derived from urogenital ridges and that their development is closely related.[2] Although these abnormalities may remain asymptomatic for a long time, patients with a solitary functioning kidney because of congenital renal abnormalities have less spare renal capacity and have an increased risk of cardiovascular and end-stage renal diseases at a young age.[16-20] Therefore, it is important to be aware of the co-occurrence of different congenital renal abnormalities in women with MDAs. However, there is still a lack of literature, clinical awareness, and standardized screening protocols. The aim of this study is to gain further insight into this co-occurrence and to estimate whether guidelines for women with MDAs should be optimized.

Materials and Methods

The present study comprises a descriptive retrospective analysis of women with MDAs who were diagnosed or treated between 1980 and 2015 at the University Medical Centre Utrecht (UMCU) in the Netherlands and was

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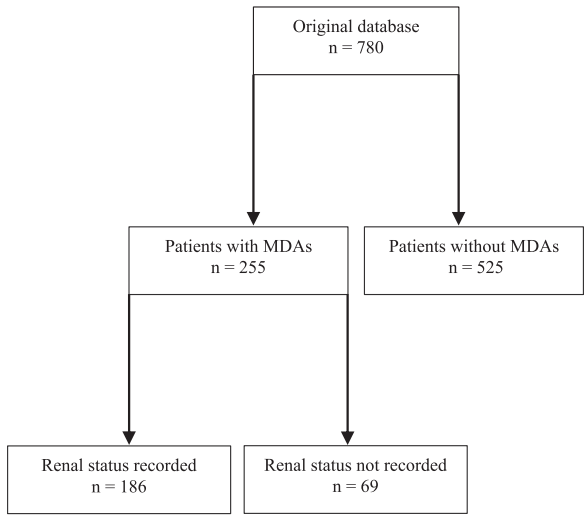
Table 1
Renal Findings in 255 Women With Müllerian Duct Anomalies (MDAs).

MDAs	Total No. (%) of Women	Renal Status Recorded (%)	Normal Kidneys (%)	Renal Abnormalities (%)
Hypoplasia/agenesis	81 (31.8)	61 (75.3)	34 (55.7)	27 (44.3)
Vaginal	1 (0.4)	0 (0.0)	—	—
Cervical	2 (0.8)	1 (50.0)	1 (100.0)	0 (0.0)
Fundal	2 (0.8)	0 (0.0)	—	—
Tubal	2 (0.8)	2 (100.0)	1 (50.0)	1 (50.0)
Combined	74 (29.0)	58 (78.4)	32 (55.2)	26 (44.8)
Unicornuate uterus	33 (12.9)	23 (69.7)	14 (60.9)	9 (39.1)
Duplex without obstructed hemivagina	63 (24.7)	42 (66.7)	25 (59.5)	17 (40.5)
Duplex with obstructed hemivagina	25 (9.8)	22 (88.0)	0 (0.0)	22 (100.0)
DES-related (duplex)	2 (0.8)	1 (50.0)	1 (100.0)	0 (0.0)
Septate uterus	19 (7.5)	9 (47.4)	8 (88.9)	1 (11.1)
Arcuate uterus	2 (0.8)	2 (100.0)	2 (100.0)	0 (0.0)
Transverse vaginal septum	13 (5.1)	13 (100.0)	9 (69.2)	4 (30.8)
Longitudinal vaginal septum	5 (2.0)	3 (60.0)	2 (66.7)	1 (33.3)
Combined vaginal and uterine septum	2 (0.8)	0 (0.0)	—	—
Nonclassifiable	10 (3.9)	10 (100.0)	1 (10.0)	9 (90.0)
Total	255 (100.0)	186 (72.9)	96 (51.6)	90 (48.4)

DES, diethylstilbestrol.

approved by the Medical Research Ethics Committee of UMCU. A research database containing 780 patients, based upon the International Classification of Diseases, Ninth Revision (ICD-9) and Tenth Revision (ICD-10), and Diagnosis Treatment Combination (DBC) codes for internal and external genital tract anomalies and renal abnormalities, was systematically analyzed for the presence of women with MDAs. MDAs were classified according to American Fertility Society (AFS) criteria.[21] However, this classification system does not cover all MDAs. To include all phenotypic manifestations of MDAs, several amendments were made. This study did not differentiate between the subclasses of unicornuate uterus and combined women with bicornuate uterus and didelphys uterus in 1 category, because it was not often clearly listed in the medical records. In addition, categories for a transversal and longitudinal vaginal septum or a combination of a vaginal and uterine septum were added. The phenotypic manifestations are summarized in Tables 1 and 2. Retrospectively, reports of the original imaging data on renal status were reviewed, and the presence of congenital renal abnormalities was recorded.

Described MDAs were diagnosed by physical examination, colposcopy (by introducing a cystoscope into the vagina), transvaginal or abdominal 2-dimensional ultrasonography, hysterosalpingography, magnetic resonance imaging (MRI), computed tomography (CT), during surgery (for example, caesarean delivery), at autopsy, or a combination of these methods. When discrepancies in MDA characteristics between different imaging methods were encountered, MRI or surgery (including autopsy) was seen as the most reliable method.[22,23] Congenital renal abnormalities were diagnosed by abdominal 2-dimensional ultrasonography, intravenous pyelography, micturating cystourethrography, MRI, CT, and dimercaptosuccinic acid (DMSA) scan, during (laparoscopic) surgery, or at autopsy. Cystoscopy or serum creatinine alone was not considered sufficient for diagnosing congenital renal abnormalities. In these cases, the renal status was classified as unknown. Data were analyzed using IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, NY).



MDAs, Müllerian duct anomalies.

Fig. 1. Flow chart of the study.

Results

Of 780 patients in the original research database, 255 women with MDAs were identified (Fig. 1). The excluded women showed anomalies such as imperforate hymen, Turner syndrome, polycystic ovary syndrome, or Bartholin's cyst. The most common MDA was duplex uterus (88/255, 34.5%), predominantly without obstructed hemivagina (63/88, 71.6%). The second and third most common MDAs were combined agenesis of the vagina and uterus

Table 2
Renal Abnormalities in 90 Women With Müllerian Duct Anomalies (MDAs).

MDAs	Renal Abnormalities	Unilateral Agenesis (%)	Multicystic, Dysplastic, or Scarred Kidney (%)	Duplicated System (%)	Pelvic Kidney (%)	Horseshoe Kidney (%)	Other (%)
Hypoplasia/agenesis	27	21 (77.8)	2 (7.4)	0 (0.0)	3 (11.1)	0 (0.0)	1 (3.7)
Vaginal	—	—	—	—	—	—	—
Cervical	0	—	—	—	—	—	—
Fundal	—	—	—	—	—	—	—
Tubal	1	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Combined	26	20 (76.9)	2 (7.7)	0 (0.0)	3 (11.5)	0 (0.0)	1 (3.8)
Unicornuate uterus	9	8 (88.9)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Duplex without obstructed hemivagina	17	6 (35.3)	7 (41.2)	1 (5.9)	0 (0.0)	2 (11.7)	1 (5.9)
Duplex with obstructed hemivagina	22	20 (90.9)	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.5)
DES-related (duplex)	0	-	-	-	-	-	-
Septate uterus	1	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Arcuate uterus	0	—	—	—	—	—	—
Transverse vaginal septum	4	1 (25.0)	2 (50.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)
Longitudinal vaginal septum	1	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Combined vaginal and uterine septum	—	—	—	—	—	—	—
Nonclassifiable	9	2 (22.2)	3 (33.3)	2 (22.2)	0 (0.0)	0 (0.0)	2 (22.2)
Total	90 (48.4)	58 (64.4)	17 (18.9)	5 (5.6)	3 (3.3)	2 (2.2)	5 (5.6)

DES, diethylstilbestrol.

(74/255, 29.0%) and unicornuate uterus (33/255, 12.9%), respectively. The least common MDA was vaginal agenesis (1/255, 0.4%). In 10 of 255 (3.9%) women, MDAs were complex and could not be classified in 1 specific category of the classification system.

Two women were included with unilateral tubal agenesis. In the category duplex uterus without obstructed hemivagina, 1 of the 2 cervices was hypoplastic in 5 of 63 women. In the category duplex uterus with obstructed hemivagina, this condition was observed in only 1 of 25 women. Uterine anomalies and reported diethylstilbestrol (DES) exposure were observed in 2 women. Five women with a longitudinal vaginal septum were included.

Renal status was recorded in 186 of 255 women (72.9%), and the other women (27.1%) did not have a retrievable renal status. Renal abnormalities were found in 90 of 186 women (48.4%) and were observed most frequently in women with duplex uterus with obstructed hemivagina (22/22, 100.0%) and in the group with nonclassifiable MDAs (9/10, 90.0%). The lowest percentages of renal abnormalities were observed in women with septate uterus (1/9, 11.1%), cervical agenesis (0/1, 0.0%), arcuate uterus (0/2, 0.0%), and uterine anomalies combined with noted DES exposure (0/1, 0.0%) (Table 1).

The most common renal abnormality was unilateral renal agenesis, which was observed in 58 of 186 women (31.2%) with MDAs and recorded renal status, and represented 64.4% (58/90) of all renal abnormalities. Unilateral renal agenesis was predominantly observed in women with duplex uterus with obstructed hemivagina (20/22, 90.9%). In 31 of 58 women (53.4%) with unilateral renal agenesis, the left kidney was affected. In 4 of 58 women, contralateral vesicoureteral reflux was present; in 2 of 58 women, a duplicated system of the contralateral kidney was present; in 2 of 58 women, a contralateral ectopic (pelvic) kidney was present; and in 1 of 58 women, a contralateral malrotated kidney was present.

The second most frequently encountered renal abnormality was a multicystic, dysplastic, or scarred kidney, which was observed in 17 of 186 women (9.1%) with MDAs and a recorded renal status, and represented 18.9% (17/90) of all renal abnormalities. In 11 of 17 women (64.7%), the left kidney was affected. In 2 women, the affected kidney was located in the pelvis. Four women in this category had an ectopic ureter, and 1 woman had an ectopic ureterocele. A duplicated system was observed in 5 of 186 women (2.7%) with MDAs and a recorded renal status, and in 5 of 90 women (5.6%) with renal abnormalities. Two women with a duplicated system had an ectopic ureterocele, and 1 woman had an ectopic ureter.

Less common renal abnormalities were a pelvic kidney (3/90, 3.3%) and a horseshoe kidney (2/90, 2.2%). Other renal abnormalities were crossed fused ectopia, unilateral vesicoureteral reflux, bilateral vesicoureteral reflux, bilateral dysplasia (asymmetrical), and bilateral hypoplasia (Table 2).

Discussion

This study presents an overview of the spectrum of female MDAs in association with different congenital renal abnormalities. Congenital renal abnormalities were observed in almost half of all women with MDAs with reported renal status, and were found most frequently in women having a duplex uterus with obstructed hemivagina. The most common congenital renal abnormality was unilateral renal agenesis, which was reported in almost two-thirds of women with renal abnormalities. However, in more than one-fourth of the 255 women in this study, renal status was not examined or reported.

The association between MDAs and congenital renal abnormalities can be explained by the fact that both genital and urinary tracts are derived from urogenital ridges. Each urogenital ridge divides into a genital and nephrogenic ridge,[2] and, in turn, the nephrogenic ridges give rise to the mesonephric ducts, also known as Wolffian ducts. The mesonephric ducts show outgrowths, referred to as ureteric buds, which form the collecting duct system and ureters[24] and induce differentiation of the metanephric blastema that forms the nephrons. Abnormal outgrowth of the ureteric buds results in renal abnormalities. Worse displacement of outgrowth concurs with the severity of the renal abnormality.[25] In addition, even though the interaction between the mesonephric ducts and Müllerian ducts is still not fully comprehended, their development occurs at the same time,[2] and the mesonephric ducts seem to affect accurate outgrowth of the Müllerian ducts,[1,26] which might explain why congenital renal abnormalities are often observed in women with MDAs. The range of different MDAs and congenital renal abnormalities seems to be attributable to the localization and time of failure in embryonic development.[25,27]

The association of MDAs, for MRKH syndrome in particular, with congenital renal abnormalities, has been described previously.[6,7,10,12,13,15] These and other previous studies including different phenotypic manifestations of MDAs have published a lower overall frequency of congenital renal abnormalities.[5-8,10-15] This finding might be explained by the fact that the present study was conducted in a university hospital, where more complex, symptomatic, and obstructive MDAs are diagnosed or treated. These MDAs are probably associated more with renal abnormalities than less complex, asymptomatic and nonobstructive MDAs.[14,28,29] The fact that women with more complex MDAs are more likely to be admitted to university hospitals might also explain why, in the current study, women with a duplex uterus with and without obstructed hemivagina or combined hypoplasia/agenesis of the vagina and uterus were observed most frequently, whereas the most common MDAs in the general population were arcuate uterus and septate uterus.[30] The prevalence of these less complex, asymptomatic, and nonobstructive MDAs could therefore be underestimated.

Renal status was not recorded in 69 (27.1%) women with MDAs, but it seems that women are screened for coexisting congenital renal abnormalities more often over time. Physicians are becoming more aware, but not all women with MDAs are screened for these renal abnormalities. However, routine prenatal ultrasound screening contributes to identifying renal abnormalities more often and in an earlier stage.

Interestingly, one would expect that women with more complex MDAs would be subjected to a more extensive screening protocol for the co-occurrence of congenital abnormalities. However, this study showed that these women were not screened more often for congenital renal abnormalities than women with less complex, asymptomatic, and nonobstructive MDAs. This finding highlights that there is still much room for improvement in the awareness of the co-occurrence of congenital renal abnormalities, even in university hospitals.

The most common renal abnormality observed in the current study was unilateral renal agenesis (64.4%). Unilateral renal agenesis was most frequently observed in women with a duplex uterus with obstructed hemivagina (90.9%), which is consistent with previous study findings.[5,8,11,14] Other renal abnormalities in women with MDAs have been studied far less often, and no significant comparisons could be made because of low numbers of observations.

Congenital renal abnormalities were not observed in women with uterine anomalies that were due to antenatal exposure to DES. Although this number is too small to draw final conclusions, the absence of renal abnormalities might be explained by the fact that the pathogenesis of uterine anomalies in these women is different from that in women with other types of MDAs.[31,32]

Evidence shows that patients with a solitary functioning kidney lack spare renal capacity and are more vulnerable to kidney-threatening conditions. These patients also have an increased risk of developing hypertension, proteinuria, and glomerulosclerosis, resulting in cardiovascular and end-stage renal disease at a younger age. Patients with bilateral congenital abnormalities of the kidney and urinary tract have an even greater risk.[16-20] Nearly 20% of all patients with congenital abnormalities of the kidney and urinary tract will need dialysis treatment by the age of 30 years. In patients with unilateral renal agenesis or renal hypodysplasia, the numbers are even higher.[17] In conclusion, although congenital renal abnormalities may remain asymptomatic for years, the long-term consequences of these abnormalities may cause a severe impairment in quality of life or may even be life threatening. Therefore, the early identification of congenital renal abnormalities is essential to improve clinical outcomes in affected women. Education plays an important role in optimizing clinical outcomes. It is highly recommended that information about several coexisting congenital abnormalities reaches these affected women early via the attending physician and patient associations to counsel them properly about appropriate treatment instead of waiting for problems in later life. Moreover, a multidisciplinary screening protocol is desirable. This study suggests starting with ultrasonography of the urinary tract to identify renal abnormalities in every woman with a recently diagnosed MDA.

Conversely, the question arises as to whether all women with congenital renal abnormalities should be routinely screened for MDAs. Previous studies reported that genital anomalies were observed in up to 60% of women with congenital unilateral renal agenesis.[22,33] To the best of the researchers' knowledge, no comprehensive studies have been performed addressing the co-occurrence of MDAs in women with all congenital renal abnormalities, rather than merely unilateral renal agenesis.

The strength of this study is the number of women included and the wide range of phenotypic manifestations of MDAs and congenital renal abnormalities that have been found. Previous studies mainly represented case reports, addressed specific phenotypic manifestations of MDAs, or

described small cohorts using incomplete MDA classification systems.

The limitations of this study are related to the classification system used, and the restrictions included variables and retrospective design, including unintentional coding errors. The presence of MDAs was not always systematically or consistently examined or reported in the medical records. There was a large variation in the imaging methods used with different diagnostic values, which were evaluated by different medical specialists over the years.

Furthermore, a generally accepted classification system that comprises all phenotypic manifestations of MDAs is still not available. The AFS classification[21] functions as a framework rather than as a comprehensively described system. This issue resulted in difficulties with classification, especially for complex and extraordinary MDAs. More recently, Acién et al[3] and Grimbizis et al[34] proposed alternative systems for the classification of MDAs. Nevertheless, these classification systems also have limitations. However, discussion about classification systems exceeds the purpose of the present study. Therefore, bearing in mind the time period (between 1980 and 2015) of the database, adjustments to the AFS classification system were made.

The present study did not take clinical symptoms of renal abnormalities or renal function into account. This study purely analyzed MDAs in association with the presence of congenital renal abnormalities. Furthermore, aside from congenital renal abnormalities, more coexisting abnormalities of different tracts are related to MDAs.[4,6-10,12,13] Although this topic exceeds the purpose of the present study, attention to clinical symptoms, renal function, and other coexisting congenital abnormalities is desirable.

Conclusion

MDAs are highly associated with congenital renal abnormalities, which were observed in almost half of all women with MDAs, most frequently in women having a duplex uterus with obstructed hemivagina. The most common renal abnormality comprised unilateral renal agenesis. However, a range of different congenital renal abnormalities was observed.

These results emphasize that women with MDAs should be routinely screened for coexisting congenital renal abnormalities. However, not all women with MDAs are screened for congenital renal abnormalities, because there remains a lack of awareness. More attention to the early identification of congenital renal abnormalities is essential to improve clinical outcomes in affected women. Whether all women with congenital renal abnormalities should be routinely screened for MDAs requires further investigation.

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