Mayer-Rokitansky-Küster-Hauser syndrome and associated malformations: are they as common as we think?

The Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome occurs in approximately 1:4,000 to 1:5,000 female live births and is characterized by congenital absence of the uterus and vagina in women with a normal female karyotype and normal, functioning ovaries. Historically, the syndrome has been classified into typical (isolated absence of the cervix and uterus) or MRKH type 1, atypical (ovarian and renal malformations) or MRKH type 2, and MURCS (müllerian aplasia, renal aplasia, and cervicothoracic somite dysplasia), which includes cardiac malformations and muscular weakness. Multiple other rare anomalies have been reported, including thrombocytopenia-absent radius syndrome, bilateral tibial longitudinal deficiency, umbilical hernia, diaphragmatic hernia, abdominal wall hernia, aplasia of the pectoralis muscle, hypoplastic sternum, and VACTERL (vertebral anomalies, anal atresia, cardiovascular anomalies, esophageal atresia, renal anomalies, limb anomalies). Familial cases and evaluation of nondiscordant twins suggest epigenetic factors, and most genetic studies have been unproductive except for the Wnt4 gene on chromosome 1, which produces the protein WNT4, an essential component for female sexual and renal differentiation as well as suppression of specific steroidogenic enzymes (17 α-hydroxylase and 3 β-hydroxysteroid dehydrogenase). Women with mutations in the Wnt4 gene tend to lack a uterus and have elevated androgens.

In 2005, Peter Oppelt and his colleagues at both the Erlangen University and Tübingen University hospitals in Germany presented very comprehensive criteria for female genital malformations called the VCAUM (vagina, cervix, uterus, adnexae-associated malformation) classification (1). The intent was to bolster a limited classification system initially proposed by Buttram and Gibbons and later revised by the American Fertility Society by assigning malformations to precise organ subgroups. It has now become the standard of classification in this area. This same group later showed when using the new VCAUM criteria that certain genital anomalies were associated more commonly with other abnormalities and confirmed that a clinical exam by an experienced gynecologist along with an abdominal and perineal/transrectal ultrasound were just as good as magnetic resonance imaging or laparoscopy in diagnosing and staging MRKH patients.

Until now, the largest studies looking at patients with MRKH have been from Germany, using a growing database from the aforementioned hospitals (2, 3). The most recent evaluation was in 2015, when 346 patients were evaluated and 47% were noted to have some associated abnormality (3). Unfortunately, for some reason, this paper does not use the VCAUM criteria, despite the use of this classification system in their prior studies. The manuscript in this month's *Fertility and Sterility* now represents the largest group of patients with MRKH evaluated in a comprehensive manner; however, from a different part of the world (4). Drs. Pan and Luo have followed a rigorous evaluation process, similar to their German counterparts, providing a VCUAM classification on 594 patients. All these patients underwent a clinical examination, ultrasound, and laparoscopy in addition to other tests based on their clinical findings. Their findings are quite startling as they show a malformation rate that is much lower than what has been reported in prior studies (Table 1).

TABLE 1

Classification of malformations in 3 studies of patients with Mayer-Rokitansky-Küster-Hauser syndrome.

VCUAM classification	Oppelt 2012 (N = 284)	Rall 2015 (N = 346) [a]	Pan 2016 (N = 594)
Vagina			
5b Complete atresia	100		100
Cervix			
2b Bilateral atresia/aplasia	100		100
Uterus			
3 Hypoplastic	0.7		0.2
4a Unilaterally rudimentary or aplastic	9.5		0.5
4b Bilaterally rudimentary or aplastic	84.2		98.5
Adnexae			
0 Normal	87		96.1
1a Unilateral tubal malformation, ovaries normal	0.4		0.3
1b Bilateral tubal malformation, ovaries normal	2.5		0.2
2a Unilateral hypoplasia/gonadal streak	3.5		0.3
2b Bilateral hypoplasia/gonadal streak	0.7		0
3a Unilateral aplasia	2.1		0.8
3b Bilateral aplasia	0		0.5
Malformations			
0 None	54.9	53.1	92.8
R Renal	29.6	26.6	5.2
S Skeletal	38	20.5	2.0
C Cardiac	3.5	2.6	0.5
N Neurologic	4.9	–	0

Note: Values presented as percent. VCAUM = vagina, cervix, uterus, adnexae-associated malformation.

[a] VCAUM classification not used, but malformation rates were listed separately.

Petrozza. MRKH and associated malformations. Fertil Steril 2016.

In reviewing these three papers, two of which presumably come from the same database, it is clear that there are some striking differences. With the two German studies, there appears to be a significant difference in skeletal abnormalities, and the paper from China shows that most patients with MRKH have no associated abnormalities. In all studies, the majority of those with an associated malformation tend to have either the skeletal or renal systems involved.

So how do we explain the low malformation rate in this most recent study? The prevailing theory has been that, at least for renal abnormalities, the close link between genital and urinary embryonal development is the key. At around the eighth week of gestation, the mesonephric (Wolffian) and the paramesonephric (müllerian) ducts begin to differentiate based on whether the ovary or testis is differentiating. The early ureters develop from the distal mesonephric duct and eventually will form into the kidney. Indeed, just as we see the relationship of renal and müllerian anomalies, there are some small case series of men with absence of the vas deferens also having an increased incidence of renal agenesis, as high as 33% (5). Is it possible that this isn't the case as we were always taught? In all studies, almost all women with MRKH have normal karyotypes and there is no evidence of at least an autosomal dominant transmission. Perhaps there is something unique among the Chinese population compared with the German population? Is it possible that epigenetic variation is so strong when it comes to urogenital development that we will see similar differences in other diverse populations?

Whatever the reason, Drs. Pan and Luo have clearly shown in their present study that associated malformation rates in women with MRKH syndrome may actually vary based on the population being studied. It is hoped that in future studies, a consistent classification system will be used, such as the VCUAM, in order to tease out different malformations based on the type of genital anomaly identified, which ultimately may give us clues to the etiology of this syndrome.

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