Complex malformations of the female genital tract. New types and revision of classification

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BACKGROUND: Complex malformations of the female genital tract are often incorrectly identified, treated and reported, probably due to not considering the malformation as a cause of the clinical symptoms and neither the embryological origin of the different elements of the genitourinary tract. METHODS: Complex malformations are studied and classified, and new types are presented. The new types of complex malformations presented are: (i) Cases of unilateral vaginal or cervico-vaginal atresia with renal agenesis and uterine duplication, with or without communication between hemiuteri; (ii) the unilateral Rokitansky syndrome; and (iii) the combination in the same patient of unilateral Rokitansky syndrome (Müllerian defect) on one side and blind vagina and ipsilateral renal agenesis syndrome (Wolffian defect) on the other side. RESULTS: A revised version of the clinical and embryological classification of genital malformations is presented and an associated diagram points out the origin of these malformations. CONCLUSIONS: These genital malformative anomalies reaffirm our hypothesis about the embryology of the human vagina as deriving from the Wolffian ducts and the Müllerian tubercle; and they show that gynecologists should be aware of the related symptoms and the embryology of the female genital tract in order to achieve a better comprehension of the malformations for their right correction or therapeutic approach.

Key words: blind vagina/cervico-vaginal atresia/genital malformations/renal agenesis/Rokitansky syndrome

Introduction

Uterine malformations are very common, and if we include minor malformations (hypoplastic and arcuate uterus), they can be observed in 7–10% of all women. However, even if we consider just the well-known uterine malformations, they are observed in 2–3% of fertile women, 3% of infertile women and 5–10% of those with repeated miscarriages (Acién, 1997).

Complex malformations of the female genital tract (and not only the uterine or Müllerian malformations) are not so common, but they do appear and are often incorrectly identified, inappropriately treated, and sometimes incorrectly reported. The main reasons for frequent diagnostic delay and/or inappropriate surgery are: (i) not considering the malformation as a cause of the patient’s clinical symptoms and (ii) not considering the embryological origin of the different constituent elements of the genito-urinary tract (Acién, 1992). Many of the cases reported in the literature have not been correctly studied or interpreted and have not been given a credible diagnosis (Acién, 2001, 2002; Gorgojo et al., 2002; Sadik et al., 2002; Mulayim et al., 2003). It is true that embryological hypotheses vary (Koff, 1933; Gruenwald, 1941; Muller et al., 1967; Forsberg, 1973; Ufelder and Robboy, 1976; Marshall and Beisel, 1978; Bok and Drews, 1983; Dohr and Tarmann, 1984; Minh et al., 1984; Mauch et al., 1985; Ludwig, 1998; Lin et al., 2002) and that the direct cause of the majority of anomalies is not known. However, the pathogenesis of the majority of them can be correctly explained and understood through the embryological hypothesis presented in Acién (1992) and other publications by us. In this article, we present three new types of malformations not previously described as such, and revise the clinical and embryological classification also presented in Acién (1992).

Materials and methods

The three new types of complex malformations studied here are: (i) cases of unilateral cervico-vaginal atresia (or only atretic hemivagina) with renal agenesis, with or without communication between hemiuteri; (ii) unilateral Rokitansky syndrome; and (iii) the combination in the same patient of unilateral Rokitansky syndrome (Müllerian defect) on one side and blind vagina and ipsilateral renal agenesis syndrome (Wolffian defect) on the other side. We show some examples of these complex malformations and in the Discussion we will revise their clinical problems. In any case, to understand them properly, it is necessary to remember and consider the embryology of the female genital tract as stated in Acién (1992).
**Cases reported**

1. **Unilateral cervico-vaginal atresia (or only atretic hemivagina) with renal agenesis**

   A case of this type, without communication between hemiuteri, is presented:

   Case 1. A 25-year-old woman came to the Emergency Unit at our Hospital with severe pains in the right iliac fossae towards the end of menstruation. The dysmenorrhea had become more intense over the last 2 years after having a laparotomy in another hospital. She had been operated on for a laparatomy and right adnexectomy because of the pain and the presence of endometriomas. At that time she was diagnosed as having a double uterus. In a posterior Computerized axial tomography (CAT) and intravenous pyelogram (IVP), renal agenesis was observed. At our hospital and after transvaginal ultrasound diagnosis of the hematometra in the right horn and absence of right blind hemivagina, we diagnosed a didelphys uterus with right cervico-vaginal atresia and right hematometra which had increased after the previous adnexectomy. We decided to carry out another laparotomy and right hemihysterectomy. During the operation we observed that the right atretic hemicervix opened into another atretic duct (see Figure 1A), and continued downwards parallel to and next to the existing normal vagina and upwards for only ~1.5–2 cm. Right hemiuterus, atretic hemicervix and the duct suggesting right atretic hemivagina and/or mesonephric duct were removed. The posterior histological study showed that this atretic duct was lined by cylindrical epithelium with areas of squamous metaplasia in the sections which presumably corresponded to the right atretic hemivagina. The left hemiuterus was moved to the center of the lower pelvis and fixed to the right round ligament. Postoperational recovery was normal. Menstruation after the operation was normal and continues to be normal without dysmenorrhea. A diagram of the genito-urinary malformation of this patient is shown in Figure 1B.

   Another two cases with communicating uteri are:

   Case 2. A 22-year-old woman, married for 2 years, with 1 previous miscarriage. She mentions that she was in hospital at age 3 due to feverish convulsions and a urinary infection. A gammagraphy and intravenous pyelogram showed left renal agenesis at that time. Later, she had new urinary infections and 1 year ago, after recurrent pain in the right iliac fossae, her gynaecologist diagnosed a double uterus. In December 2001 she came to our hospital with metrorrhagia, and the ultrasound showed a non-evolutive gestation in the left horn. A uterine curetage was carried out. The posterior hysterosalpingography (HSG) showed bicornuate uterus with communication between both hemiuteri at a low cervical level, but with the left hemicervix ending blindly (see Figure 2). The atretic left hemivagina was not identified with magnetic resonance imaging (MRI). Therefore, we believe the definitive drawing of this malformation is the one shown in Figure 2C.

   Case 3. A 34-year-old woman, 8 years of primary infertility. In 1996 she was diagnosed as having malformation and endometriosis. She had been operated on in another hospital, where they performed a left hemihysterectomy and an endometrioma in the left ovary was removed. After this, several cycles of in vitro fertilization (IVF) were carried out unsuccessfully and it was then that she came to our hospital. We managed to get the IVP and HSG from 1995 (see Figure 3A). We carried out another HSG that showed a right unicorne uterus, right hydrosalpinx and the remnants of the interuterine communication (Figure 3B). An atretic left hemivagina was not identified in the transvaginal ultrasound and we think, from the previous images, that an approximate diagram of the malformation is as shown in Figure 3D.

2. **Unilateral Rokitansky syndrome**

   Case 4. A 25-year-old woman, infertility, male factor, no symptoms. The HSG shows a unicornuate uterus and the IVP is normal, with both kidneys present (see Figure 4). Figure 4C–D corresponds to the laparoscopy showing normal left hemiuterus and adnex, while on the right side a non-cavitated rudimentary, atretic hemiuterus with normal tube and ovary are observed, as corresponds to Rokitansky syndrome, affecting the Müllerian duct on the right side only. A diagram of the malformation is shown in Figure 4E.

**Malformative combinations. Unilateral Rokitansky syndrome (Müllerian defect) and blind vagina and ipsilateral renal agenesis syndrome (Wolfian defect) on the other side**

Case 5. A 37-year-old woman, single and had never having had sexual intercourse, with obesity and hirsutism and strong dysmenorrhea lasting 10–12 days for which she was taking the pill for many years without clear improvement. She mentions that when she was born she had a cloacal anomaly for which she was operated on at 8 days of life. However, she has always suffered from certain fecal incontinence. When 12 years old, she had severe painful abdominal-hypogastric symptomatology and after several consultations with doctors she was operated on in Madrid in 1976, for ‘vaginal occlusion

**Figure 1.** (A) Right hemiuterus enlarged by hematometra with an atretical hemicervix ending in another atretic duct, probably the mesonephric duct (> >). (B) Diagram of the genito-urinary malformation observed in the patient.
and piohematometra’. According to the clinical report, ‘vaginal channelization and uterine evacuation’ were carried out. However, she has a mid infra- and supraumbilical laparotomy scar. The IVP and other image techniques showed right renal agenesis. Pains and pelvic discomfort have been permanent though they become even more intense during menstruation, which lasts many days.

The clinical examination shows the vulva and anus as basically normal, with the cloacal correction scar. The vagina presents stenosis at 1 cm, which is not permeable to a finger. The ultrasound did not provide well defined images but the uterus seemed bicornuate or didelphys, the right side being more developed. The MRI showed unicorneuate uterus, but not a proper image of the vagina. By introducing a Foley sound through the stenosis, we also managed to fill in the unicorneuate uterus and normal tube shown in the image (see Figure 5A). Due to the inverted location of the radiographic identification, it was then diagnosed as left unicorneuate uterus. The patient wanted surgery and to have all her symptoms resolved, so she eventually had a hysterectomy as she did not want nor planned to have any children in the future. Therefore, in December 2000, we carried out a laparotomy and it was possible to observe (see Figure 5C–E) a non-cavitated rudimentary left hemiuterus with normal tube and ovary, as is usually observed in the Rokitansky syndrome. On the right side, we could see a properly developed unicorneuate uterus, with a normal aspect and normal tube and ovary. A total hysterectomy of both hemiuteri was performed and it was possible to observe that the right hemicervix opened into a small and almost closed vaginal cavity in its middle third, as if it were a transverse vaginal septum. The final diagram of the malformation, as we understand it, is shown in Figure 5F. The right side would definitively correspond to a blind vagina and renal agenesis syndrome (vaginal stenosis must correspond to the opening of the blind vagina which gynecologists carried out when she had surgery at age 12); and the left side would be characteristic of unilateral Rokitansky syndrome, with normal tube and ovary and, likewise, normal left kidney. But this woman, as mentioned above, was also born with a cloacal anomaly; therefore, her complex malformation consisted of a combined Müllerian, Wolffian and cloacal (urogenital sinus) anomaly.

Results

Table 1 shows a revised version of the clinical and embryological classification of genital malformations presented in Acién (1992), now including the new types above reported. These reported malformations should be included in groups 2d, 3c and 5 of the classification presented in Table 1. Likewise, Figure 6 shows the origin of these malformations in an embryological diagram.

![Figure 2](image2.png)

**Figure 2.** Left cervico-vaginal atresia and renal agenesis with bicornuate communicating uterus. (A) HSG image. (B) MRI coronal images showing both uterine cavities and communication between them (<). (C) Diagram of the malformation.

![Figure 3](image3.png)

**Figure 3.** Left cervico-vaginal atresia and renal agenesis with bicornuate communicating uterus. (A) HSG image before operation. (B) Current HSG image. (C) IVP showing left renal agenesis. (D) Diagram of the malformation.
Discussion

From a clinical point of view, many classifications for malformations of the female genital tract have been proposed. They are based on: (i) the degree of failure in Müllerian fusion and development (Jarcho, 1946; Fenton and Singh, 1952; Buttram and Gibbons, 1979); (ii) the flaws in vertical or lateral fusion: obstructive and non-obstructive, symmetrical and asymmetrical anomalies (Strassmann, 1907; Pinsonneault and Goldstein, 1985; Rock and Schlaff, 1985; Jones, 1998); (iii) in precise aspects, such as the question of communicating uteri by Toaff et al. (1984). The general tendency is to follow

Figure 4. Unilateral Rokitansky syndrome: (A) HSG image showing left unicornuate uterus. (B) IVP, normal kidneys. (C) Laparoscopic image: left hemiuterus and adnex. (D) Laparoscopic image: right rudimentary hemiuterus (>). (E) Diagram of the malformation.

Figure 5. Genito-urinary malformation combined. (A) HSG image showing right unicornuate uterus. (B) MRI sagital images demonstrating unicornuate uterus and rudimentary vagina barely shown (>>). (C) Laparotomic observation: right normal hemiuterus (>) and left rudimentary uterus (<). Normal adnexes. (D) Normal right hemiuterus and adnex. (E) Both hemiuteri after hysterectomy. (F) Diagram of the malformation.
Table I. Clinical and embryological classification of the malformations of the female genital tract (modified from Acién, 1992).

1. Agenesis or hypoplasia of a whole urogenital ridge: Unicornuate uterus with uterine, tubal, ovarian and renal agenesis on the contralateral side.
2. Mesonephric anomalies with absence of the Wolfian duct opening to the urogenital sinus and of the ureteral bud sprouting (and therefore, renal agenesis). The ‘inductor’ function of the Wolfian duct on the Müllerian duct is also failing and there is usually: Utero-vaginal duplicity plus blind hemivagina ipsilateral with the renal agenesis, clinically presented as:
   a) Large unilateral hematocolpos*
   b) Gartner’s pseudocyst on the anterolateral wall of the vagina*
   c) Partial reabsorption of intervilaginal septum, seen as a ‘buttonhole’ on the anterolateral wall of the normal vagina which allows access to the genital organs on the renal agenesis side.
   d) Vaginal or complete cervico-vaginal unilateral agenesis, ipsilateral with the renal agenesis, and (1) with no communication, or (2) with communication between both hemiuteri (communicating uteri).
3. Isolated Müllerian anomalies affecting:
   a) Müllerian ducts: they are the common uterine malformations as unicornuate (generally, with uterine rudimentary horn), bicornuate, septate and didelphys uterus.
   b) Müllerian tubercle: cervico-vaginal atresia and segmentary anomalies such as transverse vaginal septum.
   c) Both. Müllerian tubercle and ducts: (uni- or bilateral) Mayer-Rokitansky-Kuster-Hauser syndrome.
4. Anomalies of the urogenital sinus: cloacal anomalies and others.

*These types can associate a vaginal ectopic ureter and interseptal or interuterine communication.

the classifications based on the first section (Müllerian development), which is the orientation of the classification by the American Society for Reproductive Medicine (ASRM) (1988).

However, as we reported in different previous publications (Acién and Armiñana, 1986; Acién et al., 1987, 1991; Acién, 1989, 1992, 2001, 2002), it is essential to consider the embryological origin of the different elements of the genitourinary tract in order to explain and understand the pathogenesis of any genital malformation before undertaking the best correction or therapeutical approach in each specific case. Besides, independent from the classification of the Müllerian anomalies proposed by the ASRM, we recommend a clinical embryological classification of all genital tract malformations as shown in Table 1 and Figure 6, which could lead to a better understanding and classification of complex malformations.

Indeed, it is clear that when there is absence of a whole urogenital ridge, the patient will present renal agenesis, and of all genital organs in that same side. Naturally, the absence of the hemivagina ipsilateral to the renal agenesis is not observed. Associated vertebral anomalies are sometimes observed (Acién et al., 1991).

The most complex malformations, however, tend to be those mesonephric anomalies with absence of the Wolfian duct opening to the urogenital sinus, probably due to agenesis or early and extensive lesion (from above) of the mesonephric duct. Since the ureteral bud sprouts from the mesonephric or Wolfian duct in its opening to the urogenital sinus and goes to the metanephros to form the definitive kidney, there will be renal agenesis in all distal lesions of the Wolfian duct. There will also be ipsilateral blind hemivagina, since the vagina comes from the Wolfian duct (sinuvaginal bulbs) and Müllerian tubercle (Bok and Drews, 1983; Acién, 1992). So due to the mesonephric distal lesion, its opening to the urogenital sinus will not exist either, provoking blind hemivagina. However, there is sometimes a posterior partial reabsorption of the intervilaginal septum. After careful examination a ‘buttonhole’ can be seen on the anterolateral wall of the normal vagina giving access to the genital organs on the renal agenesis side, or the longitudinal vaginal septum does not usually reach the lower third of the vagina (Acién et al., 1987). Besides this, the Wolfian duct has an inducing function on the appropriate Müllerian development (Gruenwald, 1941; Magee et al., 1979), so there will always be associated uterine malformations (didelphys, bicornuate-bicollis, or septate uterus, with septate cervix and/or communicating uteri).

These are the cases of renal agenesis and ipsilateral blind hemivagina syndrome (Acién and Armiñana, 1986; Acién et al., 1987) that can appear clinically: (i) with a large unilateral hematocolpos, or (ii) with Gartner pseudocyst: Either (a) as a blind vaginal bag holding menses and secretions and behaving as if it was a Gartner cyst communicating with bicornuate uterus (Herlyn–Werner syndrome), or (b) as a simple cyst in the anterolateral upper third of the vagina associated to, but not communicating with, a bicornuate uterus. In these cases, it is actually a septate or bicornuate uterus with two cervices, but the hemicervix of the Gartnerian pseudocyst side is atretic and the hemiuteri are communicate, simulating a bicornuate-unicollis uterus. Evidently, if the vaginal or cervico-vaginal atresia on this side is complete we will have cases as reported in this paper in point 1: Unilateral cervico-vaginal atresia (or only atretic hemivagina) with renal agenesis (with or without communicating uteri). And, if there is also atresia or hypoplasia of the corresponding hemiuterus, we would have the cases published as ‘uterus unicornis with rudimentary horn and ipsilateral renal agenesis’ (Acién, 1992; Stolzlechner et al., 1995; Heinonen, 1997); at other times the rudimentary horn is caviteted, with hematometra (Shukunami et al., 2000).
Occasionally, a duct ending in the hemicervix of the blind side can also be seen in the HSG, and this can correspond to a remnant of the mesonephric duct, and also to an atretic ectopic ureter (see Acién et al., 1991, 2004). In other cases there is a single ectopic ureter associated to any of the previous types. In these cases there may be no agenesis but renal hypoplasia, and such an ectopic ureter may end in the blind hemivagina (Acién et al., 1990), or the ectopic ureter ends at the top, ramified in fibrous tracts. There could even be different atretic ectopic ureters coming from the same mesonephric duct (Bhandarkar et al., 1997). The further from the site where the ureteral bud normally sprouts, the more dysplastic the kidney formed in the metanephros and induced by the ureteral bud is; therefore the anomaly can then range from dysplasia to complete renal agenesis.

For some years, there have been reports on cases of a simple ectopic ureter opening into the Gartner duct cyst with ipsilateral renal hypoplasia and dysplasia (or agenesis) (Curiarino, 1982; Gotoh and Koyanagi, 1987), or in hydrocolpos (Constantinian, 1966), or in duplicated Müllerian ducts (Gilsanz and Cleveland, 1982), probably with insufficient surgery and varied embryological interpretations (Borer et al., 1998; Wu et al., 2001; Petit et al., 2002) and usually reported by pediatrics (Wakhlu et al., 1998). Some of these ducts could already be a mesonephric remnant in which an atretic ectopic ureter could open.

Isolated Müllerian anomalies can also be induced by a minor mesonephric defect. In any case, such Müllerian anomalies can affect:

1. The Müllerian ducts: the different utero-tubaric anomalies are presented in the classification by the American Society for Reproductive Medicine (1988). Some recently reported rare cases of complex Müllerian malformation should be included here, such as a case with a hypoplastic non-cavited uterus and two rudimentary horns (Sadik et al., 2002), and others with isolated cervical atresia with no vaginal atresia (Deffarges et al., 2001). All of them would be cases with segmentary atresia of the Müllerian ducts by spot lesions. We must bear in mind that the existence of a cavitated rudimentary horn can also behave as a complex malformation and provide serious clinical problems or differential diagnosis with other pathologies.

2. The Müller tubercle is a collection of paramesonephric cells placed caudally to the terminal paramesonephric bud and seen in the medial wall of the mesonephric ducts (Gruenwald, 1941; Marshall and Beisel, 1978; Dohr and Tarmann, 1984). Thus, the Müllerian tubercle is below the caudal tip of the uterine primordium and above the dorsal wall of the urogenital sinus, with the mesonephric ducts lying laterally. This and the mesonephric ducts (sinuvaginal bulbs) later form the vagina (Bok and Drews, 1983; Acién, 1992). Therefore, those anomalies affecting just the Müllerian tubercle can originate total or segmentary vaginal atresia, or a transverse vaginal septum. More complex cases are those which show cervico-vaginal agenesis with present uterine body as well as the rest of the upper genital tract.

3. Both Müllerian tubercle and ducts. In such cases atresia or utero-vaginal agenesis characteristic of the Rokitansky syndrome may occur. But this can also sometimes appear with a cavitated rudimentary horn causing retrograde menstruation, endometriosis and significant clinical problems (Acién et al., 1988; Malik et al., 1997). In other cases, as demonstrated in Case 4 reported here, unilateral Rokitansky syndrome can exist, which would indicate an alteration on one side only of the Müllerian ducts and probably of the corresponding part of the Müllerian tubercle. A similar case has been reported by Pasini et al. (2001), which presented a ‘spontaneous ectopic contralateral pregnancy with unicornuate uterus’, whereas other cases such as that of Mulayim et al. (2003) ‘unicornuate uterus and unilateral ovarian agenesis associated with pelvic kidney’ really correspond to what we indicated as agenesis of everything derived from a urogenital ridge. Sometimes, gonadal dysgenesis and Rokitansky syndrome can be associated (Guittron-Cantu et al., 1999; Aydos et al., 2003), and this can also be associated to other pathologies (Raybaud et al., 2001), but cases such as that of Gordo et al. (2002) (‘Gonadal agenesis 46XX associated with the atypical form of Rokitansky syndrome’) cannot be understood. If there is gonadal agenesis (not posterior loss through twisting or similar) it must be due to agenesis of the gonadal ridge which is situated on the urogenital ridge. As has been presented, it is usual for everything derived from the urogenital ridge to be missing, including the kidney. It would be, therefore, bilateral renal agenesis (Potter syndrome), which is incompatible with life (Devriendt et al., 1997).

With regards to the anomalies of the urogenital sinus, the most common is the unperforated hymen, but we must also consider the cloacal (anus–vulva) anomalies, frequently combined with other higher anomalies. Indeed, a final group, and perhaps the most complex malformations, would be those malformative combinations which associate Wolffian, Müllerian and cloacal alterations, as in Case 5.

Conclusions

The malformative anomalies shown reconfirm our hypothesis on the embryology of the human vagina as derived from the Wolffian or mesonephric ducts together with the Müller tubercle (Acién, 1992).

All lesions of the mesonephric duct are associated to unilateral renal agenesis and utero-vaginal anomalies. If the lesion is distal, blind hemivagina with hematocolpos can be observed; if it is higher, a Gartner pseudocyst can be observed in some cases, while in others, there is vaginal or complete cervico-vaginal agenesis. At the same time, both anomalies can have: (i) communicating uteri (apparently there is a bicornuate or septate uterus), or (ii) non-communicating uteri and then retrograde menstruation, endometriosis and/or unilateral hematometra (if the tube is closed) are eventually observed.

The Rokitansky syndrome would be an exclusively Müllerian anomaly of the ducts and Müller tubercle. There is no renal agenesis and it can be unilateral. Also, there can be alternating Müllerian and Wolffian or mesonephric malformative combinations with respect to the affected side. It could be a Müllerian anomaly in one side
(unilateral Rokitansky syndrome), and in the other, a mesonephric anomaly with blind hemivagina and ipsilateral renal agenesia.

Therefore, gynecologists must be aware of:

Every clinical suggestion of genital malformation. Attention to long-lasting intra- and postmenstrual dysmenorrhea which does not improve with the pill, to metrorrhagia or persistent postmenstrual spotting (occasionally very malodorous), to endometriosis, specially in youth (Acien, 1986; Acien et al., 1992), to obstetric problems and abnormal presentations, etc. Knowledge of the genito-urinary embryology that best explains the malformative anatomic findings, and To make a careful clinical examination and transvaginal ultrasound.

To ask for and to carry out hysterosalpingography and i.v. pyelogram, as well as CAT, MRI and anything needed to clarify a complex malformation.

To carry out a detailed and appropriate laparoscopic or laparoscopic observation when needed, and

To think about and act on the malformation according to embryological deductions, trying to correct only what is necessary to avoid present and likely clinical manifestations.

References


Dohr G and Tarmann T (1984) Contacts between Wolfian and Müllerian ducts and their interactions when needed, and

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