MALFORMATIONS OF THE FEMALE GENITAL TRACT AND EMBRYOLOGICAL BASES

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Abstract:
Female genital tract malformations are frequently a cause of reproductive problems. Besides, complex malformations also frequently generate serious gynecological problems, often ones with inappropriate surgical solutions, as the gynecologist does not think of the malformation as either the cause of the symptoms or of its embryonary origin. Apart from analyzing the embryological bases in the development of the female genital tract and insisting on the well known müllerian origin of the uterus, the ratification of the embryological hypothesis about the origin of the human vagina from the Wolff ducts and the Müller tubercle allows us to not only advance in knowledge but to use that knowledge for better clinical management of the problems generated by the complex malformations of the female genital tract.
In this review we study the methods and means for the diagnosis of female genital-urinary malformations, their classification and clinical findings, and especially those cases involving unilateral renal agenesis, vaginal ectopic ureter and other complex malformations. We also analyze the related obstetric and gynecologic pathology, and especially that cases of complex genital malformations. We review the related literature and some interesting case reports, as well as our experimental studies in rats. After re-asserting our hypothesis about the embryology of the human vagina as derived from the Wolff ducts and the Müller tubercle, we suggest different recommendations for a better approach and management of the malformations of the female genital tract according to the findings observed in different diagnostic procedures.

Key words:
Malformations of the female genital tract, complex malformations, embryology, embryology of the vagina, renal agenesis, blind vagina, müllerian anomalies, mesonephric anomalies.
Introduction

The malformations of the female genital tract include those anomalies affecting the development and morphology of the Fallopian tubes, uterus, vagina and of the vulvar introitus, with or without ovarian, urinary, skeletal or other organs’ associated malformations. Most of the malformations affect the uterus, and are, therefore, referred to as mullerian anomalies, but sometimes they are of mesonephric or wolffian origin, apart from the fact that many alterations of the mullerian system also have their origin in a mesonephric anomaly.

The malformations of the female genital tract are frequent but not always detected. Uterine anomalies have been reported in 0.1-3% of women, in 4% of infertile women and in 15% of those with recurrent miscarriage [1]. Most likely, an increase in the use of the ultrasound, hysterosalpingography (HSG), magnetic resonance (MR), hysteroscopy and laparoscopy has led to an apparent increase in their incidence. We have observed that if minor uterine anomalies (hypoplastic and arcuate uterus) are included among the malformations, the frequency of those uterine malformations reached 7-10% in all women. But even just considering those uterine malformations properly recognized clinically (bicornuate or septate uterus), they were observed in 2-3% of fertile women, 3% of infertile ones and 5-10% of those with recurrent miscarriages [2].

Complex malformations of the female genital tract (and not only the uterine or mullerian malformations) are not as common, but they do appear and are often incorrectly identified, inappropriately treated, and sometimes incorrectly reported. The main reasons for the frequent diagnostic delay and/or inappropriate surgery are: 1. Not considering the malformation as a cause of the patient’s clinical symptoms, and 2. Not considering the embryological origin of the different constituent elements of the genito-urinary tract [3]. In our opinion, many of the cases reported in the literature have not been correctly studied or interpreted [4,5]. However, given that these anomalies frequently cause very important clinical symptoms, and 2. Not considering the embryological origin of the different constituent elements of the genito-urinary tract [3]. In our opinion, many of the cases reported in the literature have not been correctly studied or interpreted [4,5]. However, given that these anomalies frequently cause very important clinical problems, with specific symptoms, an appropriate knowledge of the embryology of the female genital tract is essential to solve the symptoms and start the treatment appropriately [3,6-8]. We will see that there are patients with agenesis of all the derived organs from the urogenital ridge (therefore, the kidney included), but the most complex cases of malformations in the female genital tract include those with syndrome of renal agenesis and ipsilateral blind hemivagina [9]. In this syndrome, there is occasionally renal hypoplasia with an ectopic ureter in the blind hemivagina, and other times there is no complete blind hemivagina but a partial reabsorption of the intervaginal septum. All these cases support the theory that the human vagina would embryologically derive from the mesonephric or wolffian duct with the participation of the Müller tubercle. And though it is true that embryological hypotheses vary [8,10-20] and that the direct cause of the majority of anomalies is unknown, the pathogenesis of the majority of these malformations can be correctly explained and understood through our embryological hypothesis that, as we will see later, likewise provides the guidelines for its appropriate correction.

Etiopathogenesis of the malformations of the genital tract

The direct cause of genital malformations is unknown despite the many different theories and hypotheses in this area. The familiar incidence is difficult to research though it is clear that it does exist [21]. The karyotype is generally normal [22] but sometimes there are mosaicisms or other anomalies that do not seem related to the malformation (the patient with didelphys uterus shown in figure 11B has a karyotype 46XXq+q+ informed as “without clinical consequences”); and the environmental causes can only explain some cases. Apart from the DES-syndrome, other teratogenic drugs, malnutrition, metabolic alterations, viral infections and placental anomalies have been implied. Association of didelphys uterus and trisomies 13-15 has been described, some familiar cases seem to be linked to a recessive autosomal gene and others to a dominant autosomal one [23]. In cases with hereditary renal adysplasia (HRA) (a rare autosomal dominant condition frequently associated to pulmonary hypoplasia and renal agenesis [24]) a balanced 6p/19q traslocation supporting the assignment of one of the loci for HRA to chromosome 6p has been described [25]. In others cases the anomaly is part of a more general malformative syndrome: the MURCS association, the uterus-hand-foot syndrome with characteristic dermatoglyphes [26], the Klippel-Feil anomaly (fused cervical vertebrae), the Winter syndrome (middle ear anomalies), Fraser, Meckel, Rudiger and Edwards and Gale’s [27], Greene et al [28] and Duncan et al [29] speculated that the combination of mullerian duct, renal and skeletal anomalies seen in the MURCS association is due to a teratogenic event late in the fourth week of fetal life, when the cervicothoracic somite mesoderm and pronephric duct are in close proximity. Others [30] still believe that a teratogenic event occurring before the end of the first month of fetal life is the best explanation for other major anomalies sometimes linked to MURCS association.

It seems then that genital malformations are influenced by multifactorial, polygenic and familiar mechanisms that together can create a favorable environment for the anomaly. But in most cases there is no evident cause or association. Discordant congenital anomalies of the reproductive system in monozygotic twins have been described [31]. However, the embryological development of the genital tract and the chain of anatomical events leading to the production of the malformation are better known, and therefore, we must analyze the embryology for a better understanding of the pathogenesis.

Embryological bases for the development of the female genital tract

The gonads begin to develop when the embryo has a crown-rump length (CRL) of 5-7 mm, in the fifth week of pregnancy. Their formation begins as swellings located on either side of the dorsal mesentery, at the ventromedial surface of the mesonephros (Wolf’s body), and they become prominent in the coelomic or peritoneal cavity [32]. The longitudinal swelling on both sides of the primitive mesentery, which encloses the mesonephros and the
of the extracellular matrix during the migration [35]. Since primordial germ cells and fibronectin and other components in addition, there is a close association between the yolk sac, attracted by a chemotactic factor [34] or teloferon. Gonocytes or germ cells arrive at the gonadal ridge from the mesenchyme and overlying coelomic epithelium [33]. The genital ridge early in development, and also from the mesonephric cells, which migrate into the area of the mesonephric or Wolffian ducts; MD, paramesonephric or Müllerian ducts; GR, go

The somatic cells of the gonads are derived from (germ cells) that migrate from the backside of the yolk sac. The somatic cells of the gonads are derived from mesonephric cells, which migrate into the area of the genital ridge early in development, and also from the mesenchyme and overlying coelomic epithelium [33]. The gonocytes or germ cells arrive at the gonadal ridge from the yolk sac, attracted by a chemotactic factor [34] or teloferon. In addition, there is a close association between the primordial germ cells and fibronectin and other components of the extracellular matrix during the migration [35]. Since the gonocytes XX arrive at the gonadal ridge later than the XY gonocytes (around the 10th-12th week), the wave of primary sexual cords have already passed and form the rete ovarii in the medullary region of the gonad. Now, in the absence of Y chromosome, HY antigen and TDF/SRY gene (but probably in the presence of HX antigen), the secondary sexual cords include each gonocyte individually in the cortical region of the gonad, generating primordial follicles and the cells of those cords differentiate into granulosa cells [3,36]. Follicles fail to form in the absence of oocytes or with loss of germ cells, and oocytes not encompassed by follicular cells degenerate.

The internal genitals begin their formation in the sixth week. In the thickness of the urogenital ridge, the mesonephric excretory tubules converge in a mesonephric or Wolffian duct that descends to the cloaca in the urogenital sinus. A longitudinal invagination of the celomic epithelium is formed on the outer side of the urogenital ridge and originates the paramesonephric or Müller’s duct. This one, at the top, opens into the celomic cavity, descends in parallel, and externally to the mesonephric ducts, crossing them ventrally, growing in the caudomedial direction until fusing in the Y-shaped middle line forming the uterine primordium, without reaching the urogenital sinus. The lower parts of the paramesonephric or Müllerian ducts diverge and fuse with the medial wall of the mesonephric ones inside a common basal membrane, and then, caudal to the end portion of the Müllerian ducts, over the dorsal wall of the urogenital sinus, an accumulation of paramesonephric cells which constitute the Müller tubercle [3] can be observed. This Müller tubercle is then delimited laterally by the Wolff ducts [11,15,17]. These mesonephric or Wolffian ducts getting closer medially, they do open into the urogenital sinus, and from the caudal tip of their opening, the ureteral bud sprouts in each side and, growing laterally, anteriorly and cranially, moves toward the metanephros to form the definitive kidney.

When the ovary is being formed, and therefore the testosterone and the anti Müllerian hormone (AMH) are absent, the Wolffian ducts become atretic and the Müllerian ones develop. The fused caudal parts of the paramesonephric ducts form the uterus, and the tubes come from the uppermost part. However, the adequate development and fusion of the paramesonephric ducts, the reabsorption of the separation septum and the correct formation of the normal uterus are induced by the laterally situated mesonephric ducts. These act as guide elements for the paramesonephric ducts [11,37] [Fig. (2)]. The Müller tubercle’s cells remain below the uterus, and at both sides of it, a peritoneal folds which from the fused paramesonephric ducts move laterally towards the lateral walls of the bony pelvis, are known as the broad ligaments. The ovaries are located on the posterior surface of the broad ligaments.

The development of the urinary system is intimately associated with that of the genital tract and occurs between the sixth and ninth week [12]. The metanephrogenic mass is formed in the intermediate mesoderm, caudally to the mesonephros, and is induced by the metanephric diverticulum or ureteral bud that has sprouted from the dorsal side of the mesonephric duct in its opening into the urogenital sinus. The ureteral bud forms the ureter and from its cranial part it expands to form the renal pelvis in the metanephrogenic mass. However, the bladder and the urethra sprout from the urogenital sinus and adjacent mesenchyma, though the ventrocena
el part of the bladder comes from the allantois. After division of the cloaca by the urorectal septum, the formation of the rectum and superior anal duct dorsally and of the urogenital sinus ventrally occur [38]. In the inferior part of the urogenital sinus, in front of the urorectal septum, the mesonephric ducts open.
and the bladder, which incorporates the allantois, is formed ventrally. Gradually, the bladder ascends and the most caudal part of the mesonephric ducts with the ureteral bud (what has been named the “Wolffian patch” [39]) ends up incorporated into the dorsal wall. Like this, the ureters are incorporated and remain, opening themselves separately, in the vesical trigone. Now, the growing of a new urogenital fold finally separates the bladder and the urethra anterior and ventrally, while the mesonephric ducts continue opening into the lower side of the urogenital sinus (see figure 2B).

The vagina is the female genital organ whose embryology is more controversial. There are theories that suggest it derives from the paramesonephric ducts [14,40], from the mesonephric or Wolffian ducts [41], from the urogenital sinus [18], or from a combination of these structures [19,42]. Until very recently, the most generalized theory about the embryology of the vagina suggested that its upper part comes from the Müller ducts (müllerian vagina) and the lower part from the urogenital sinus (sinus vagina) [12,43], though always assuming the inducing function of the mesonephric ducts in the appropriate müllerian development [11,37].

However, apart from the inducing role of the mesonephric ducts on the Müllerian ducts, different studies, some of them experimental, have proved their participation in the formation of the vagina, so that the “protrusions of the sinus” or the “sinuvaginal bulbs” observed during the development of the vagina would actually be the caudal segments of the Wolffian ducts [16,19,44,45]. Certainly, Hart [46] had already adopted the term “Wolffian bulb” because the epithelial pockets that form the sinuvaginal bulbs keep remnants of the Wolffian ducts. Witschi [47] re-examined Koff’s embryos and deduced that the sinuvaginal bulbs were identical to the lower segments of the Wolffian ducts. This observation was confirmed by Bok and Drews [16] in an experimental study with embryo cultures.

These findings, together with the analysis of published papers [48-54], as well as cases studied by us [9,55-57], especially those referring to patients with renal agenesis and ipsilateral blind hemivagina, led to our proposal of an embryological hypothesis [3,56]: “The vagina seems to come completely from the fused mesonephric ducts, though the Müller tubercle would also take part and is fundamental for its adequate formation and cavitation”. According to this embryological hypothesis, the fused Müller ducts would form the uterus until the external cervical orifice,

Figure 2. Development of the female genital ducts. A, frontal view, 7-8 weeks. B, lateral view, 9-10 weeks. MD, paramesonephric or Müllerian ducts; WD, mesonephric or Wolffian ducts; MT, Müllerian tubercle; UW, urogenital wedge; URS, urorectal septum (From Acién, Hum Reprod 7:437-445, 1992).

Figure 3. Hypothesis of the embryological development of the human vagina. MD, paramesonephric or Müllerian ducts; WD, mesonephric or Wolffian ducts; MT, Müllerian tubercle; US, urogenital sinus; UB, ureteral bud; U, ureter (From Acién, Hum Reprod 7:437-445, 1992).
induced by the mesonephric ducts that descend at both sides and to which they caudally fuse after their divergence. Later, the mesonephric ducts regress cranially but from the level of cervical os, they enlarge and form the sinuvaginal bulbs, incorporating the Müller tubercle’s cells to the vaginal plate formed by the fusion of both bulbs [Fig. (3)]. Likewise, the Müller tubercle would be delimited at the top and laterally by the Müller ducts, more laterally by the Wolffian ducts, infero-laterally by the portion of the sinuvaginal bulbs and below by the urogenital sinus [39]. The posterior cavitation of the Müller tubercle let the Müllerian cells line the primitive vaginal cavity with a cuboidal or paramesonephric epithelium. Then, by metaplastic induction or, more probably, by epidermization from the urogenital sinus, the vagina becomes lined by a flat, squamous, polystratified epithelium. Some mesonephric remnants may remain in the vaginal wall, which occasionally can give rise to Gartner cysts [39], though we will later see we should discard the possibility of an atretic blind hemivagina.

This hypothesis has also been proved experimentally in rat embryos by our group [39] [Fig. (4)], as we observed that the protrusions of the sinuses or the sinuvaginal bulbs are positive for specific immunohistochemical markers for Wolffian derivatives (GZ1 and GZ2) and that in posterior stages of the development, these structures show themselves all along the completely formed vagina. Fig. (5) shows in A) the classical diagram of the formation of the vagina from the Müller ducts and the urogenital sinus. In B) the diagram of our embryological proposal after these experimental studies.

Since the ureteral bud sprouts from the opening in the urogenital sinus of the mesonephric duct, the absence or distal injury of a duct would mean the absence of the ureteral bud and, therefore, the definitive kidney would not develop either, which will result in renal agenesis in that side and in blind or ipsilateral atretic hemivagina. In these cases, mesonephric and paramesonephric remnants are frequently found in the intervascular septum and are identified as such by the characteristics of the epithelium that lines them [7,57,58]. Suidan and Azoury [58] pointed out that the epithelium of the vagina and of the transverse vaginal septum are from a mesonephric origin. Certainly, the epithelium that covers the blind hemivagina has müllerian characteristics (cuboidal) [51,59,60] except when there is some communication with the permeable side or inflammation; in these cases, it is epidermoid, squamous, stratified and flat. And when the blind vagina is atretic, small, found in the anterolateral upper part of the normal hemivagina and lateral to the cervix (Gartner pseudocyst, Herlyn-Werner Syndrome and Wunderlich Syndrome), then the epithelium is of a mesonephric kind, probably due to the absence or non-participation of the Müller tubercle [7,9,57] [Fig. (6)]. Besides, in cases of blind hemivagina there is generally an associated uterine malformation (normally a duplicity) because of a failure in the inducing function of the injured mesonephric duct.

In summary, then: 1) The appropriate development, fusion and reabsorption of the separating wall between both Müller ducts is induced by the Wolffian ducts placed at both sides and which act as guide elements. 2) The fused Müller ducts form the uterus until the external cervical os, and the inducing mesonephric ducts regress cranially though they enlarge caudally from the level of cervical os, form the sinuvaginal bulbs, incorporate the Müller tubercle’s cells and give rise to the vaginal plate whose cavitation is lined by Müllerian cells with a cuboidal or paramesonephric epithelium. Then, by metaplastic induction or by epidermization from the sinus, the vagina is lined by a flat, squamous, stratified epithelium. 3) Since the ureteral bud sprouts from the Wolffian duct in its opening into the urogenital sinus, the absence or distal injury of one of these ducts will give rise to a renal agenesis and blind or ipsilateral atretic hemivagina and a uterine anomaly (fusion
or reabsorption defect) due to a failure in the inducing function of the injured mesonephric duct.

The development of the external genitalia begins in the fourth week with the formation of the genital tubercle in the ventral portion of the cloacal membrane, but the final aspect is not established until the twelfth week. Genital swellings and urogenital or urethral folds appear on each side soon after, and between both folds is the urogenital groove and membrane. The genital tubercle forms the phallus, which in absence of male inductors becomes the clitoris, while the genital folds form the labia majora. The urogenital or urethral folds do not fuse and form the labia minora. The urogenital groove remains open hence forming the introitum, where the urethra, and later the vagina, will open after the fenestration of the urogenital membrane; and the remnants of that membrane will be the hymen [61].

Means and methods for diagnosis of the female genital malformations

Although we will later insist on the diagnostic methodology when analyzing the clinical manifestations in the case of genital malformations, we are going to see here the main means of diagnosis to be considered and applied, always according to the case, whenever there is a suspicion of genital malformation:

1) First, logically, we must make a good history and general and genital physical examination. A primary amenorrhea with or without cyclical pelvic pain, a postmenstrual metrorrhagia, dyspareunia, late or recurrent miscarriages, premature deliveries, breech presentation, etc, should suggest a genital malformation that will later be confirmed or not with a careful genital exam. The inspection of the vagina and the cervix using speculum and visualizing vaginal (attention to paravaginal cysts) or cervical anomalies, the vaginal or rectal examination detecting two uterine horns or tumors, or the check-up of the genital channel after delivery observing septum or a double uterine cavity suggest malformation and guide the diagnosis.

2) The ultrasound examination is of great diagnostic help since it enables us to detect the presence or absence of two uterine bodies, the shape of the uterus, or menstrual retentions related to hematocolpos, hematometra, hematosalpinx and endometriosis. Besides, it guides the existence of obstetric pathology (breech, transversal presentation) or the existence or absence of a kidney, which should be systematically searched for if we suspect genital malformation. Currently, most uterine malformations may be suspected and almost be catalogued very closely with the transvaginal ultrasound exam (in systematic longitudinal and transversal slices). It is not the most adequate method for the differential diagnosis between bicornuate and septate uterus, however with both the transvaginal and the abdominal ecography in transversal slices, the fundal perimetrial indentation over the line linking the tubal orifices can be measured and therefore the uterine anomaly can be catalogued [62,63]. The sonohysterography has also been suggested as a means of differential diagnosis between the bicornuate and septate uterus, thus eliminating the need of laparoscopy [64]. Likewise, the three-dimensional ultrasound has been recommended [65] and it has shown a good correlation with the laparoscopic findings in 92% of the patients.

3) The hysterosalpingography (HSG) [66,67] is the most specific, sensitive and generalized technique at our disposal for the diagnosis of uterine anomalies (the gold standard), although it is limited to provide just one profile of the cavities connecting with the exterior. An isolated (cavitated or not) uterine horn, for example, cannot be proved with the HSG, but we will have the image of a unicornuate uterus. Attention must be paid to the possibility of another hemicervix that may not have been detected or channelled, and that may actually be before a septate, bicornuate-bicollis or didelphic uterus, any of them with a double vagina. In such cases, two uterine injectors or cannulas must be used if possible, and a simultaneous image of both cavities must be taken [Fig. (7)]. The differential diagnosis between bicornuate or septate uterus cannot be done with the HSG, though there may be suspicion when valuing the width of the angle between both uterine horns (< or > 90º C), with the inner border more straight than bent in the septate uterus.

4) The intravenous urography adequately informs us of the possible presence of an associated anomaly of the urinary tract. This occurs in approximately 30% of women with genital malformation and, therefore, it should be performed in all cases. Nevertheless, pyelocalitical duplications,
ureteral ectasia, renal ptosis, etc are very frequently found anomalies, also found in women without any genital malformation. Unilateral renal agenesis is, however, systematically associated to a genital malformation, and thus its finding guides or confirms the diagnosis of agenesis in all the derivated organs of a urogenital ridge or the existence of a ipsilateral blind hemivagina.

5) Spine X-rays. Some malformations, especially when there is agenesis in all the derivatives of a urogenital ridge, may equally present skeletal anomalies (scoliosis, vertebral block, etc).

6) The **laparoscopy** (or laparotomy) is an important element of diagnosis in genital malformations, especially in the group of agenesis or hypoplasias. Besides, it increases the diagnostic accuracy on the HSG image and it is essential to distinguish between a septate or bicornuate uterus, to evaluate the presence and characteristics of a possible rudimentary horn and of the ovary contralateral to that of a present unicorneuterus and shown in the HSG, and to check the existence of an associated pelvic pathology (adherences, endometriosis) or of tubal anomalies.

7) The **hysteroscopy** is as well an effective diagnostic and therapeutic method, though of limited value, in the detection of congenital anomalies. It has a special interest in the case of septate/subseptate uterus, to observe and remove the intrauterine septum, but it is not the gold standard in the diagnosis of uterine malformations as some authors suggest [68].

8) The **cystoscopy** is valuable to differentiate the renal and ureteral agenesis from a possible secondary atrophy or involution, especially when the renal shadow and the descendent vias do not appear in the urography. Likewise, the cystoscopy is valuable in order to investigate cases with an ectopic ureter.

9) The **Magnetic Resonance Imaging** (MRI) of the pelvis is the most innovative but expensive technique, and its real value for routine use is under study. For the specialists in diagnosis by imaging it is the gold standard and, of course, in some cases it is essential for the diagnosis (cervico-vaginal atresia cases [see Fig. (8)]), but in most patients the transvaginal ultrasound is sufficient, and above all the HSG image. Several publications have proved the MRI’s diagnostic accuracy and the correct classification of the anomalies, making laparoscopy unnecessary in double uteri, unicornuate uterus, Rokitansky syndrome, etc, and therefore being cheaper. In some anomalies, it may be of great help in the planning of surgical therapies. Nevertheless, it does not provide us with information about the tubal condition or the presence of endometriosis without endometriomas and, for example, the presence of fistulae/as or interuterine or intervaginal communication areas, or the presence of communicating uteri that may be related to unilateral cervico-vaginal atresia and renal agenesis are not properly evidenced. All this seems to be easier to prove with the HSG (see figure 8A).

10) In some malformations it may be of help to utilize the **computer axial tomography** (CAT) and in others, we must resort to a **colpography**, well directed (i.e in girls, filling with vesical catheter and eventual retrograde filling of vaginal ectopic ureter) or also after puncture and injection of contrast agent in blind hemivaginas [Fig. (9)]. With the retrograde filling of the blind side, the corresponding hemiuterus, a possible ectopic ureter opening into the blind vagina or the transeptal communication can be observed [69]. In some cases, a **combination of techniques** may be required, as the chromo-pertubation or, in cases of vaginal agenesis, a HSG by laparoscopic puncture of the uterine body with injection of contrast agent (figure 9B). In this case the diagnosis was proved without risks.

11) The general blood analysis does not provide us with any information related to malformations, but some cases do require a **chromosomal study**. And of course, in case of surgical removal, the anatomy of the malformation in the surgical piece should be studied, as well as an **histological study** of the septal tissues, of the lining epithelium, etc,
should be carried out. All this will allow a better understanding of the anomaly.

**Classification and clinical findings in female genito-urinary malformations**

From the clinical point of view, many classifications have been proposed according to: A) Functional aspects based principally on the potential capacity of the uterine cavity and its musculature [70]. B) Degree of failure in the fusion and müllerian development [49,71,72]. C) Defects in the lateral and vertical fusion [73]: obstructive or non-obstructive, symmetrical or asymmetrical anomalies [74-77]. or D) Punctual aspects, as the matter of communicating uteri [78,79]. The most frequent classifications have those based on the müllerian development, and therefore we should speak about the following [Fig. (10)]:

1. Anomalies by total or partial agenesis in one or both Müller ducts: unicornuate uterus, Rokitansky syndrome.
2. Anomalies by total or partial absence of fusion: didelphic uterus, bicornuate (bicollis and unicollis) uterus.
3. Anomalies by total or partial absence of reabsorption of the septum between both Müller ducts: septate and subseptate uterus.
5. Segmentary defects and combination of the different anomalies.

Buttram and Gibbons [71] and Buttram [80] introduced a classification of the müllerian (uterine) anomalies, which, with few modifications, was adopted and recommended for its general use by The American Fertility Society [81] (currently, American Society of Reproductive Medicine, ASRM). The ASRM [81] considered seven basic groups, analyzed basically from the point of view of the müllerian development and their relationship to fertility (see figure 10B): I. Agenesis and hypoplasias; II. Unicornuate uteri; III. Didelphic uteri; IV. Bicornuate uteri; V. Septate uteri; VI. Arcuate uteri; and VII. Anomalies related to DES Syndrome; and it proposed a protocol-sheet in which general use is recommended in order to achieve uniformity in the communication of results. The additional findings referred to the vagina, cervix, Fallopian tubes, ovaries and urinary system must be pointed out.

However, it would seem preferable, because of its simplicity, to speak about anomalies by agenesis (Types I and II), lack of fusion (Types III and IV), absence of reabsorption (Type V) and lack of posterior development (Type VII), though taking into account that: 1) We consider the arcuate uterus as a minor form of the bicornuate uterus, although in the ASRM classification it is rather a kind of subseptate uterus and sometimes it can be so. 2) Any depression in the uterine bottom, on its outer surface, makes the depression then to be included as a bicornuate uterus and not septate, since in this case the external shape of the uterus is supposed to be normal and uniform. 3) Many cases are transitional (fusion and reabsorption partial failures). The cataloguing of a case [Fig. (11)] is sometimes difficult because the upper part is bicornuate (fusion defect, practically didelphys) and is clearly septate (reabsorption defect) lower down (figure 11A). And the other way around, we can also find a septate bicervical uterus. 4) The uterus is didelphic when there are two hemiuteri completely detached, at least up to the cervices, where they may be touching each other. But, as already mentioned, there are
also cases with double uterine body and istmic portion, but with simple exocervix and vagina. They are anatomically and clinically didelphic uteri, as shown in figure 11B. 5) We agree with Musset’s bidirectional theory [82,83] on the reabsorption of the uterine septum, since when there are communicating uteri, they are generally communicating at an istmic level and besides, this is always the weakest part of the septate. The explanation to this is in the different portions of the Müller ducts which give rise to different uterine portions and, specifically, to the convergence in the internal cervical os of the Müller ducts with distal divergence up to the external cervical os [39]. 6) The septate or double vagina is associated to a didelphys and bicornis-bicollis uterus, but also to a septate uterus; and the vagina can be septate even in the presence of a normal uterus or of non-septate or septate uterus with a double cervix [84-89].

In 1979 Magee et al [37] suggested a new embryological classification of the genito-urinary malformations based on the observations that syndromes of the mesonephric duct induced müllerian anomalies. In this same sense, we believe that the theory suggested by Acién [3,7,56] on the embryology of the vagina, as stated in the embryological bases, should be the correct one and, consequently, a clinical-embryological classification that considers all the elements of the genito-urinary tract should be considered. This would allow an embryological justification for all the malformations, including the most complex cases, as we will later see. Therefore, taking that embryological hypothesis as a basis, we have suggested the following classification of malformations of the female genital tract [3,6]:

1. Agenesis or hypoplasia of a whole urogenital ridge. There will be absence of kidney, functioning ovary, tube, hemiuterus and hemivagina (undetectable) in that same side [90]. It can also associate with vertebral and/or auditive anomaly.

2. Mesonephric anomalies with absence of the Wolffian duct opening to the urogenital sinus and of the ureteral bud sprouting. There will be renal agenesis and ipsilateral blind vagina, and usually, uterine anomaly due to the absence of the “inductor” function of the injured mesonephric duct on the Müllerian duct (uterine duplicity with/without interseptal or interuterine communication). If there is an ectopic sprout of the ureteral bud, there could then be renal hypoplasia and ectopic ureter opening into the blind vagina. These are the most complex malformations and can appear:
   A) With large hematocolpos in the blind hemivagina.
   B) With Gartner’s pseudocyst in the anterolateral wall of the permeable vagina.
   C) With partial reabsorption of the intervaginal septum seen as a buttonhole on the anterolateral wall of the permeable vagina.
   D) With complete unilateral vaginal or cervico-vaginal agenesis.

3. Isolated müllerian anomalies, can affect:
   A) Paramesonephric or Müllerian ducts: uterine and/or tubal anomalies, sometimes segmentary. Unicorne, bicornuate, didelphic, septate uterus and others.
   B) Müllerian tubercle: vaginal (or cervico-vaginal) agenesis or atresia, and segmentary atresias as the transversal vaginal septum.
   C) Both Müllerian tubercle and ducts: Mayer-Rokitansky-Kuster-Hauser Syndrome (uni or bilateral)

4. Anomalies of the urogenital sinus. Imperforated hymen with persistent urogenital membrane, cloacal anomalies and others.

Figure 12. Diagram showing the embryology of the female genital tract and the places for the origin of the five groups of malformations pointed out in the text. WD, Wolffian duct; MT, Müllerian tubercle (From Acién et al, Hum Reprod 19:2377-84, 2004).
5. **Malformative combinations**: mesonephric anomaly on one side and müllerian on the contralateral side and eventual associated anomaly of the urogenital sinus. Fig. (12) shows a diagram of the embryology of the female genital tract and the places where the five groups of malformations mentioned above originate.

Logically, the **clinical findings** in malformations of the female genital tract will depend on the type of anomaly and on its association or lack of association with other anomalies of the genital tract or extragenital anomalies. But it must be taken into account that many women with malformations may be asymptomatic. Others, however, suffer from a wide range of symptoms and problems that may appear at any age (from childhood to old age) and in any condition (pre- or post-menarche, single or married, during gestation, delivery or puerperium, pre- or post-menopause). In general, the symptoms depend on the type of anomaly and the age of the patient. For its better understanding we will follow the above mentioned embryological classification as well as that of the ASRM [81] for Müllarian anomalies:

1. **Agenesis or hypoplasia of a urogenital ridge**.

   Clinically, the behavior is the one corresponding to the unicorunate uterus without the presence of a rudimentary horn or adnex (tube and ovary) on the opposite side [91-93]. It sometimes presents associated skeletal [94] and/or auditory [95] anomalies.

2. **Mesonephric anomalies**.

   We will see their clinical findings in a posterior section involving unilateral renal agenesis and cases of vaginal ectopic ureter as complex malformations.

3. **Müllerian anomalies**.

   - **Transverse vaginal septum**. It corresponds to a transversal constriction or a short segmentary atresia of the vagina that may obliterate it totally or partially, the transverse septum being then imperforated or perforated. In this case, it presents through annular stenosis, sometimes so narrow that it may originate menstrual retention and dysmenorrhea, or dyspareunia or more probably, soft-tissue dystocia at the moment of delivery. Certainly, it is frequently confused with a complete effacement of the cervix, that does not dilate, therefore looking like a puntiform external cervical os, and even so, the dilatation of the cervical os may be complete. The introduction of a contrast agent through the orifice (sometimes, a dot) on the vaginal bottom obtaining an HSG image can clearly prove the transverse vaginal septum.

   The vaginal complete transverse septum, or imperforated, can present in the girl as an hydrometrocolpos that produces several complications derived from the compression [96-99]. In other cases it may not present symptoms until puberty, when the hematocolpos forms itself, with episodes of pelvic pain and primary amenorrhea similar to vaginal atresia. It will also be studied in a posterior section on complex malformations.

   - **UTERINE ANOMALIES** (see figure 10A). We will analyze these anomalies following the ASRM [81] classification:

     **Class I (agenesis or hypoplasia): Ia** (vaginal agenesis with a functional uterus and endometrium). They are usually complex malformations with the external genitals and the tubes appearing normal. The uterus may be normal or present fusion or reabsorption defects, and the cervix may be present, absent or be hypoplastic [100,101]. It is an uncommon and rare anomaly; we have dealt with some cases with segmentary vaginal atresia and the one shown in figures 8B and 9C with complete cervico-vaginal atresia. After puberty, the primary amenorrhea may be the only symptom, but there is usually cyclical pelvic pain that worsens with time. Physical examination reveals normal external genitals, absence of a vagina and, in the rectal examination, a present, normal or thickened uterus, with or without pelvic tumors corresponding to hematometra, hematosalpinx or endometriosis. **Ib** (cervical agenesis). Its presence with a functioning endometrial cavity and normal vagina is extremely rare. The symptoms are similar to those of anomalies in Ia. In some cases, the primary amenorrhea or the infertility have been the only reason for consultation. Naturally, if there is a functioning endometrial cavity, the problem is the severe dysmenorrhea and/or cyclical cryptomenorrhea [102]. **Ic** (uterine fundal or corporal agenesis). Very rare; the only symptomology is the primary amenorrhea and infertility. Physical examination usually shows a hypoplastic cervix, without opening, and the palpation reveals a very small uterine body. The (abdominal or transvaginal) ultrasound and eventually the laparoscopy confirms the diagnosis, though this one could be done with the pelvic examination alone. **Id** (tubal agenesis). It is also very rare and is normally associated with agenesis of the ovary and the corresponding hemiuterus and, therefore, with renal agenesis. There could exist, however, segmental tubal agenesis, which, if bilateral, naturally generates infertility. **Ie** (combined utero-vaginal agenesis). It is the most frequent type of agenesis and corresponds to the Rokitansky-Kuster-Hauser syndrome [103-105]. In this syndrome, the tubes and ovaries are usually normal, though they may be absent in one of the sides and being then associated with renal agenesis. Other renal anomalies (renal ptosis, pelvic kidney) are frequent. In the laparoscopy, a fibrous tract or two solid rudimentary horns are generally observed. Some of these rudimentary horns may occasionally present a small functioning endometrial cavity, giving rise to retrograde menstruation and endometriosis [106,107]. Patients usually consult due to primary amenorrhea, difficulty in sexual intercourse or infertility. They can also present cyclical pelvic pain if there is functioning endometrium present.

   The physical examination in these class I anomalies shows normal external genitalia but absent vagina, sometimes with the aspect of a small bag or depression in cul-de-sac at 1-2 cm from the introitus and the placing of a normal speculum is even possible after reiterative sexual intercourse and pressure, but when the pressing stops it is clearly seen that there is no vagina. The rectal examination shows the absence of a uterus, some small nodular structure or a tumor corresponding to an endometroma or pelvic kidney. The abdominal ultrasound helps in the diagnosis, but this is clearly established with the laparoscopy and, currently, with the transrectal ultrasound and/or the MRI.

   Uterine, skeletal, auditory and other associated anomalies [28,108-114] are described in patients with these ASRM class I anomalies (mainly, Rokitansky syndrome). Likewise, cases of segmentary müllerian atresias consisting of bilateral blind uterine horns with a small endometrial cavity, a separate cervical remnant and total
vaginal agenesis associated with distal extremity abnormalities have been described [115].

**Class II (unicornuate uterus):** This class corresponds to the proper development of one of the Müllerian ducts, with poor or no development of the other side. Therefore, the unicornuate uterus can be: IIA. With cavitated and communicated rudimentary horn. It would actually be a bicorneate uterus with scarce development of one of the horns. Attention must be paid since it could be two communicating uteri and what happens in the less developed side is that its corresponding hemicervix is atresic; it would be associated then with a blind hemivagina also atretic and with ipsilateral renal agenesis. IIB. With cavitated and non-communicated rudimentary horn. Obviously, there will be retrograde menstruation (or hematometra if the tube was atresic or a tubal sterilization was performed). And if the cavitated rudimentary horn corresponds to an atretic hemivagina or cervico-vaginal atresia in that same side, there will be renal agenesis as well [116]. IIC. With solid rudimentary horn. In these three cases, the corresponding tube and the ovary of the affected side are usually normal, though it can be a unilateral Rokitansky syndrome [6]. But there can also be blind atretic hemivagina and, therefore, renal agenesis. IID. Without rudimentary uterine horn. Frequently, there is neither a corresponding tube nor an ovary, or they are hypoplastic and then there would be an associated ipsilateral renal agenesis (agenesis of all the derivatives of the urogenital ridge) with skeletal anomalies or of the bony pelvis [117]. But in the laparoscopy or laparotomy, attention must be paid in case it is an acquired unilateral adnexal absence (i.e. after torsion and necrosis). Other times, there is a rudimentary horn, though it does not come out from the uterine fundus but converges in the cervical portion with the hemiuterus normally developed as if it was (and it is) a didelphys uterus where one of the sides is atretic, just like when is it so in both sides in the Rokitansky syndrome. It presents a normal Fallopian tube and ovary on the side of the atretic hemiuterus and, naturally, there is no renal agenesis. We have described it as unilateral Rokitansky syndrome and therefore, it would be solely a Müllerian anomaly [6].

The problems related to the unicornuate uterus are essentially fertility and pregnancy related (miscarriages, premature deliveries, breech presentations, etc) and we will discuss them later. In the cavitated rudimentary horns, communicated or not, there can be gestation with a possible uterine rupture, usually at the end of the second trimester. Frequently, the medical history is completely normal and the symptoms depend on the presence of an obstructive anomaly, with the possibility of developing hematometra, hematosalpinx and endometriosis. One of our cases with an uncommunicated cavitated rudimentary horn only developed hematometra and a strong dysmenorrhea appeared after the performance of a bilateral tubal sterilization in another hospital. The patient, after two previous normal deliveries, was diagnosed as missed abortion in the third gestation and a curettage was performed. After the procedure, the doctor informed her that she should be operated on due to leiomyoma. In the laparotomy, the same doctor did not observe any leiomyoma but “bicorneate uterus” and performed a bilateral tubal sterilization after previous declaration of the patient of not wishing to have any more children. This is where the severe symptoms of the patient started, with strong dysmenorrheas and visits to the Emergency Services of our hospital at every menstruation. The performance of a HSG showing unicornuate uterus clarified the situation, which was solved by total hysterectomy considering the patient’s expressed wish [Fig. (13)].

In patients with AFS class II anomalies, the physical examination must suggest unicornuate uterus if we find the uterine body very laterally diverted; and in the opposite side a pelvic mass can be palpated or it may look like a leiomyoma or a bicornuate uterus. The HSG is decisive for the diagnosis of unicornuate uterus, but the laparoscopy and the transvaginal ultrasound (and eventually the MRI) are necessary to make clear the presence and characteristics of the rudimentary horn or the absence of the derivatives of the urogenital ridge on that side. In the transvaginal ultrasound we must suspect unicornuate uterus when we observe in the transversal cuts that, if we move the sound towards the uterine fundus, the endometrium only moves towards one of the horns, ending as a spearhead towards the horn instead of ending in a T-shape or more or less curved in the uterine fundus. However, attention must be paid since the laparoscopic appearance may even be the one of a normal or asymmetric bicornuate uterus. A differential diagnosis can be stated with all these possibilities.

**Class III (didelphys uterus).** It presents two completely detached hemiuteri (like two unicornuate uteri) with two cervixes and a double vagina. Apart from the problems related to fertility (the reproductive performance of women with didelphys uterus is similar to the performance of women with unicornuate uterus [118]), the only symptom can be dyspareunia due to trip with the vaginal septum during sexual intercourse, but it is not frequent either. The vaginal examination shows the longitudinal vaginal septum and, in the bottom and at each side, normal or small cervixes. In the bimanual examination, two detached uterine masses can be felt. The HSG is the most appropriate diagnostic procedure and, if possible, it must be performed simultaneously with a double cannula (see figure 7A). The abdominal and transvaginal ultrasound, and eventually the laparoscopy, confirm the diagnosis upon showing the uterine bodies completely apart. Two detached uterine bodies both showing the ultrasound characteristics described for the unicornuate uterus can be observed in the

![Diagram of the malformation showing the right cavitated uterine horn non-communicating with the left side and which caused an hematometra with severe dysmenorrhea after tubal ligation.](image)
transvaginal ultrasound. Some cases of didelphys uterus are associated with a blind hemivagina with hematocolpos, hematometra, hematosalpinx and endometriosis (and, of course, ipsilateral renal agenesis), though this happens more frequently in bicornuate and septate uterus. There are transitional cases (as one shown in the HSG in figure 11B) in which, being the uterine body actually one of a didelphys uterus, the lower part of the cervical channel, the external cervical os and the vagina are simple. This was observed both in what is shown in the HSG and in the laparoscopic observation of two completely detached hemiuteri. Maybe it should be included as bicornis-unicollis uterus, but this is anatomically and clinically didelphys, and that was the clinical behavior in this case.

**Class IV (bicornuate uterus).** If the müllerian fusion is partial, a bicornuate uterus originates, but the detachment between both uterine horns may continue up to the cervix (that would be the bicornis-bicollis uterus, usually with double vagina due to longitudinal vaginal septum) or the detachment affects only the uterine body (bicornuate-unicollis uterus) or there may even remain only a small fundal central depression (that would be the arcuate uterus, to be considered separately). There is also the possibility of a bicornuate uterus with septate cervix and simple vagina or also septate vagina, or, as we have seen above in the didelphys uterus, this one can be so with simple exocervix and vagina. Except for the possible dyspaurenia due to vaginal septum, or the presence of an associated blind hemivagina, the only symptomatology of the bicornuate uterus is the one related to obstetric and fertility problems. In the physical examination a bicornuate uterus can be palpated, but the diagnosis is usually suggested by the abdominal ultrasound and, especially, by the transvaginal one. In the transversal cuts we can observe two endometrial areas that detach significantly, together with the uterine bodies, if we move upwards to the fundus with the sound. Likewise, a bicornuate uterus must be suspected if a fundal perimetrial indentation is found below the straight line linking the tubal horns or if it is less than 5 mm above it [62,63]. The HSG (which must be performed simultaneously in both cavities, with two cannulas, in the case of bicornis-bicollis uterus) is even more specific and demonstrative, and it will show a separation over 90° in the image of both uterine bodies. Regardless of proper differential diagnosis with the septate uterus, it should be better confirmed by laparoscopy showing the separated prominence of both uterine horns. On the other hand, we would be before a septate uterus. Currently, however, the sonohysterography, the tridimensional ultrasound imaging and the MRI may help or be enough for the differential diagnosis.

**Class V (septate uterus).** It is a lack of reabsorption of the septum (or intermediate wall) between both Müllerian ducts after fusion. Therefore, the uterus (just the endometrial cavity) will be totally (septate uterus) or partially divided (subseptate uterus) by a longitudinal septum or intermediate wall. The septum sometimes affects the vagina as well. As in patients with bicornuate uterus, these malformations are also asymptomatic except for obstetric and fertility problems. There are described cases of septate uterus, septate cervix and double vagina with bilateral gestation [119]. The physical examination may show a vaginal septum and septate (sometimes bicervical) cervix [120-122], but the uterus is normal in the bimanual examination. The ultrasound will show little separation between both endometrial areas in the transversal cuts as we move upwards to the fundus and absence of fundal perimetrial indentation; the HSG will show a separation angle between the image of both endometrial cavities smaller than 90° and have straight rather than curved inner edges; the hysteroscopy will show the septum; and in the laparoscopy, the uterine perimetrial fundus without depression will be observed. All these techniques allow for a correct diagnosis. The differentiation with the bicornuate uterus is basically made through laparoscopy, though the shape of the uterine fundus sometimes raises doubts. We have already mentioned that the sonohysterography, the tridimensional ultrasound and the MRI can also help or be enough [64]. Homer et al [123] have performed a major revision on the management and reproductive outcome of the septate uterus.

**Class VI (arcuate uterus).** It has already been mentioned that from our point of view it is a minor form of bicornuate uterus, but it could also be a minimum subseptum. The diagnosis is suspected by means of a systematic transvaginal ultrasound (transversal slices, curved fundus) and with the HSG, the hysteroscopy and the laparoscopy. There are no other findings apart from the reproductive problems [124,125], although some authors have not observed such problems in the arcuate uterus.

**Class VII (DES syndrome related anomalies).** T-shaped hypoplastic uterus with an extremely small uterine cavity, cornual constrictions and bulbous dilatation of the lower segment are included here [Fig. (14)]. It can be associated with menstrual irregularities (hypo or oligomenorrheas) and infertility. Cervical ridges, folds or ectropion with a “glans” aspect, pseudopolyps or cervix hypoplasia may be observed. The diagnosis is made by HSG. Here, the ultrasound is less useful (though it may be suspected in it) and the laparoscopy usually shows normal internal genitals. We include the T-shaped hypoplastic uterus, which do not generally seem related to the DES syndrome, in the ASRM class VII group. From the clinical point of view, anyway, most cases are asymptomatic, though sometimes, as mentioned above, there may be frequent hypomenorrheas and infertility. In some of our cases, a lateral fundal pregnancy transformed into a missed abortion has behaved

![Figure 14. HSG images showing DES related uteri (Class VII of ASRM).](image)
as a cornual or interstitial ectopic one with no possibility of removal by uterine curettage.

- Tubal anomalies
These anomalies are rarely observed without an associated uterine anomaly, except for those cases with bifid, uni or bilateral tube, which are relatively frequent as casual findings in laparoscopy or laparotomy, without symptoms, consequences or complications. The bilateral tubal agenesis is very rare and would be included in the ASRM class I group (agenesis/hypoplasties). Other times there are tubal segmentary agenesis and the resulting problems are infertility or ectopic pregnancy.

4. Anomalies of the cloaca, urogenital sinus and external genitalia.
- Imperforate hymen. It is the absence of fenestration of the urogenital membrane in the opening of the vagina into the urogenital sinus. It is not usually associated with other anomalies of the genital system. When puberty comes, it causes hematocolpos (cryptomenorrhea) that, contrary to the one caused by the inferior vaginal agenesis or transverse vaginal septum, is observed in the introitus as a bump on the hymenal membrane often showing a bluish color [Fig. (15)]. The periodic cyclic pain does not appear as early as in the vaginal agenesis. The physical examination is enough to give a diagnosis and immediately perform the incision of the hymen and empty the hematocolpos.

- Cloacal dysgenesis, including the persistence of the urogenital sinus [126-130]. The wrong partition of the cloaca by abnormal development of the urorectal septum is uncommon, at least from what is observed in published cases, but the incidence of associated genito-urinary anomalies is high. The five most important types of cloacal or anorectal malformations are: 1) The rectum-cloacal fistula; 2) The rectum-vaginal fistula; 3) The rectum-vestibular fistula; 4) The imperforate anus and 5) The ectopic anus. The rectum-cloacal fistula, with a persistent cloaca, can go from a shared wide channel to an only fistulous way to drain the urinary, genital and intestinal tracts. In the rectum-vaginal fistula, the vestibule may seem anatomically normal but the anus is not observed in the perineum. The defect is probably the result of an anorectal agenesis due to an incomplete subdivision of the cloaca.
- Several irregularities of the urethra and the genitalia can be found in the presence of a persistent urogenital sinus. And the disorders of the urinary tract associated with persistent urogenital sinus may include the urethral duplication, the renal and unilateral ureteral agenesis or atresia or the pelvic kidney, although we have already mentioned that there are associated genital anomalies in the cases of unilateral renal agenesis. There possibly exist, as well, cases of urethral and vesical duplication, described as patients with an ectopic ureter ending in a Gartner cyst, as we will see later. - Anomalies of the external genitalia. In normal women, on the other hand, two somewhat frequent anomalies can be observed: labial fusion and labial hypertrophy. The true labial fusion as a defect in the early development of the middle parts (usually not fused) of the urogenital folds, is much less frequent than a posterior fusion due to inflammatory-type reactions. And the labial hypertrophy can be uni or bilateral and may require posterior surgical correction in certain cases if it is a nuisance for the woman.
Previously, Woolf and Allen [157] had stated the frequent, simultaneous occurrence of congenital malformations of the reproductive and urinary tracts, and Marshall and Beisel [15] had described the association of uterine and renal anomalies in the ACI rat model, spontaneously occurring defects of partial uterine agenesis and renal agenesis, and pointed out that “a mesonephric duct defect appears responsible for these anomalies”. This syndrome is usually associated with a didelphys, bicornuate or septate uterus and includes other syndromes described in literature that related renal agenesis and Gartner cyst (Herlyn-Werner [158], Wunderlich [159] syndromes, etc.). They may arise in two ways:

1. With hematocolpos (in girls, hydrocolpos) [96,97,160-162]. It is generally made manifest by progressive intra- and post-menstrual dysmenorrhea present from menarche, though it is frequently diagnosed at 17-18 years of age. The young woman usually reports cyclical menstruations but with the mentioned intra- and post-menstrual dysmenorrhea, and in the examination a lateral and anterior bulge of the vagina is observed that makes it impossible to reach the cervix. This bulge is the hematocolpos, sometimes containing over a liter of black blood or chocolate fluid. At bimanual exam, a great low and lateral pelvic tumor or mass is felt, apart from the fact that there can also be unilateral hematometra (uncommon) and more frequently, hematosalphinx and endometriosis. If it is suspected, the ultrasound helps the diagnosis very much, and the pyelography (and cystoscopy), when showing renal agenesis, allows for a diagnostic confirmation. Likewise, the transvaginal puncture lets the drainage of the chocolate blood and the injection of a contrast agent to radiologically visualize the great blind vagina and retrogradely fills the corresponding hemiuterus and tube [Fig. (16)]. The performance of a laparoscopy should already be planned and will show bicornuate uterus and possible hematosalpinx (in one of our cases, twisted), endometriosis, etc. Sometimes, malposition of the ovary is observed [163]. In the same surgical act, we should perform a resection of the separating wall between the permeable and the blind vaginas with removal of the hematocolpos. In the fundus, the two cervices can now be observed. Sometimes there is the antecedent that when the painful menstruation ends, the patient expels abundant dark blood. It can correspond to the rupture of the septum [164] with the consequent creation of communicating uteri, generally at an isthmic level. Other times, the communication between the permeable and the obstructive sides appear to be there from the beginning, and several previous publications have reported the frequent association of communicating uteri and urinary disorders [82,83,165,166]. Or the communication can be observed in the vaginal fundus or at a low cervical level, being evidenced with the retrograde filling after puncture of the blind vagina. In these cases, in which there exists a communication between the permeable and the blind side, the presence of post-menstrual persistent metrorrhagia is characteristic. Typically, it becomes very malodorous from the moment the young woman starts having sexual intercourse since the “blind vaginal bag” becomes infested through the communicating orifice with that retained menstrual content. This foul smelling is perceived as well by the family living with the woman and occasionally as such is referred by the mother. Hematosalpinx does not usually occur in these patients, but bilateral adnexitis frequently does. Some of our cases have made their debut as an abortion in the same blind vagina, there existing complete uterus-vaginal duplicity [56]. Nygren and Persson [167] also reported a similar case.

It must also be pointed out that there can exist an ectopic ureter opening into the blind vagina [69]. Naturally, in these cases, there is no renal agenesis but a severe renal hypoplasia that is neither visualized in the pyelography nor in the cystoscopy (and, in our case, it was also missed by the CAT report). It is made manifest then by unilateral hydrometrocolpos, but since the communication between both sides is frequent (in our case at the level of the vaginal fundus), the symptom is permanent urinary incontinence between normal micturitions. The puncture and injection of contrast agent in the blind hemivagina allowed for the identification of the ectopic ureter by retrograde filling.

![Figure 16](image-url) Images obtained from patient with right blind hemivagina syndrome with great hematocolpos and ipsilateral renal agenesis. A, right renal agenesis in the i.v. urography. B, image of the blind vagina filled with contrast agent after its puncture. C, ultrasound image. D, laparoscopic image showing the right retrouterine bulge due to distension of the blind hemivagina with hematocolpos. E, left adnex. F, bicornuate uterus. G, hematocolpos drainage. H, intervaginal septum.
Finally, in some patients with renal agenesis and ipsilateral blind vagina, a partial reabsorption of the inter vaginal septum could have occurred. Such cases are similar to the didelphys uterus with double vagina, but typically the inter vaginal septum does not reach the inferior third of the vagina, or there exists a buttonhole on the lateral wall of the vagina that allows access to the genitalia of the side where the renal agenesis is [Fig. (17)]. In some of our cases and in others published [168], patients had some important problems in childhood due to vesicoureteral reflux in the single kidney.

2.- With Gartner pseudo-cyst. Frequently there is no other symptomatology than the one related to fertility problems. Sometimes, there is dysmenorrhea and chronic pelvic pain. In the examination, a cystic mass with the appearance of a Gartner cyst can be observed in the upper half or third of the right or left anterolateral wall of the vagina. It actually is an atretic blind hemivagina associated with renal agenesis [169]. The corresponding hemicervix is usually atretic and the HSG can show the image of a bicornuate-unicollis uterus since it is about communicating uteri. In other cases, with the same hysterographic image, we can also appreciate that the atretic hemicervix is permeable, fistulous and is communicated with the atretic blind vagina as shown in Fig. (18). It corresponds to the above mentioned Herlyn-Werner syndrome [158]. The outstanding symptom in these patients is a “sudden leukorrhea”, occasionally malodorous. The inspection with the speculum may seem normal (in several consultations), but if the supposed Gartner cyst is pressed (perhaps very flaccid) a mucous and/or purulent secretion will flow through the cervix. Of course, the HSG and the i.v. urography clarify the diagnosis.

3.- In other cases, the uterus is unicornuate, with atresia of the hemiuterus of the obstructive side, or the atresia only affects the corresponding hemicervix, without communicating uteri. Then there will be hematometra, hematosalpinx and endometriosis in the blind side [Fig. (19)]. Naturally, the i.v. urography, the ultrasound and the laparoscopy will also clarify the diagnosis, though we must bear in mind the malformation for its appropriate diagnosis. Our proposal is to consider them separately in the following subgroup:

* Vaginal or complete cervico-vaginal unilateral agenesis. It is ipsilateral with the side of the renal agenesis. As we mentioned in the classification, there can be communication between both hemiuteri and they may behave then as a bicornuate unicollis uterus (communicating uteri). In other cases of unilateral cervico-vaginal atresia there is no communication between the hemiuteri and we have then the cases with unilateral hematometra and endometriosis due to retrograde menstruation in the side of the absence of a vagina and kidney [170,171]. Segmentary müllerian atresia (unicornuate uterus with two cavitated, non-communicating rudimentary horns) in that unilateral cervico-vaginal atretic hemiuteri has also been described [172]. Both Nisolle and Donez [173] and ourselves [174] wrote about this in a letter.
to the editor of Human Reproduction. The case in Fig. (20) is very demonstrative and interesting since it shows the Müller duct (hemiumerus with atretic cervix) opening into or ending in what must be the mesonephric duct and the blind vagina.

- **Vaginal ectopic ureter**

Sometimes it is an unilateral double ureter, one of them ending ectopically in the vesical neck, urethra, introitus or, less frequently, in the vagina, cervix or uterus [175-183]. However, many times there is a simple ectopic ureter opening into a single vagina, or more probably, into a blind hemivagina [184-186]. As the ureteral ectopia appears with renal dysplasia, increasing in severity as the higher the exit of the ureteral bud is from the mesonephric duct, many of these cases of vaginal ectopic ureter are associated with severe degrees of renal dysplasia or agenesis, with the only presence of the ureteral remnants [38,187-189].

If there is any renal functioning, the outstanding symptom is urinary loss or incontinence between normal micturitions. The dysplastic kidney, however, is not usually drafted in time for the i.v. pyelography (apart from a certain renal ptosis) and it is normally cataloged as **renal agenesis** by the urographic findings. In the cystoscopy, only the ureter coming from the normal kidney can be observed; fistulae are not observed and, therefore, the girl’s urinary incontinence is frequently attributed to psychological problems or similar.

As stated above, the ectopic ureter may end in a simple vagina, though there is always a certain deformity or smudge in that side of the vagina; and usually ends high (vaginal fornix or cervix). So there is severe renal dysplasia or agenesis and the incontinence or urinary loss is little evident. In one of our cases it was made manifest by pain in the right iliac fossa and fever (ascending infection from the remnant ureteral duct), having previously had an operation for appendectomy. Usually, however, the ectopic ureter is associated with a blind hemivagina (unilateral imperfective vagina, atretic hemivagina of Gartner pseudocyst type and uterine duplication) into which it opens. In such situations, an hydrocolpos is originated in the girl until, primitively or secondarily, a communication is established with the side of the permeable vagina and then the permanent urinary incontinence between normal micturitions occurs. After menarche, what we referred to above for the blind vagina with ipsilateral renal agenesis syndrome will occur. As it can be observed in Fig. (21), the ectopic ureter seems to end into the cervical portion of the side corresponding to the blind hemivagina, but if it is analyzed more closely then we will see the only or some ectopic ureters end into a duct that must be the mesonephric or the wolffian one, and this itself reaches the blind hemivagina. In other cases there seems to exist as well some mesonephric remnant or remnant of the atretic ectopic ureter [190]. The diagnosis can be easily established (apart from what was referred above for the blind hemivagina cases), achieving the retrograde filling of the ureter in a direct colpography when closing the vaginal entrance by traction over a balloon catheter [182,191], or in the case of a blind hemivagina, by puncturing and filling it with a contrast agent. As mentioned before, we believe that some published cases of ectopic ureter in cysts of the Gartner duct [192-204] actually correspond to cases of unilateral blind hemivagina with an ureteric ectopia, other cases correspond to ureteroceles [205,206]; and others, as those two reported by Dwyer and Rosamilia [5], probably are anomalies of the urogenital sinus (cloaca-allantois) with doubling of bladder and urethral meatus and where the supposed Gartner’s duct cyst must be in fact a hemibladder [207]. If this is so in the cases by Dwyer and Rosamilia, the ureter would not be ectopic and the urethral fistula defect would be just an incomplete duplication of the urethra.

![Figure 20. Case of patient with right cervico-vaginal atresia and renal agenesis without communicating uteri. A. Laparotomic observation: right hemiuterus enlarged by hematometra and normal left hemiuterus with corresponding normal adnex. B. Right hemiuterus enlarged by hematometra with an atretic hemicervix ending in another atretic duct, probably the mesonephric duct (>). C. Sectioned right hemiuterus showing the cervical atresia, the supposed mesonephric duct and the atretic vagina. Hematometra. D. Diagram of the genito-urinary malformation observed in the patient (modified from Acién et al, Eur J Obstet Gynecol Reprod Biol 117:249-251,2004).](Image)

![Figure 21. A. Hysterosalpingography carried out through the permeable vagina (>>) and showing the left blind vagina (*), the supposed mesonephric duct (>) and the ectopic ureter (<<). B. Final diagram of the reported genito-urinary malformation (modified from Acién et al, Eur J Obstet Gynecol Reprod Biol 2004;117:105-108).](Image)

- **Crossed renal ectopy**

Results when the ectopic kidney goes through the middle line and rests on the side opposite to that of its ureteral origin [Fig. (22)]. It is probably due to early renal fusion during the embryonal period and when the ascending of the kidneys takes place, the dominant one pulls the ectopic. Almost always there is malrotation and skeletal, genital,
cardiovascular and gastrointestinal system anomalies often coexist [208]. Purpon [209] showed the existence of cases with crossed renal ectopy with solitary kidney as an exceptional finding. However, Cranitis and Terhort [210] reported case number 25 in the world literature, and later there have been several communications [211,212] stating the existence of multiple genitourinary anomalies and associated skeletal anomalies.

- **Transverse vaginal septum**

The incomplete transverse vaginal septum is made manifest by annular stenosis of the vagina that may originate dysmenorrhea, dyspareunia and, more likely, dysostias of the soft channel at the moment of delivery. The complete or imperforate transverse septum, however, can be made manifest in the girl by hydrometrocolpos which generates severe complications derived from the compression or, in other cases, it may not have any symptoms until puberty in which an hematoocolpos is formed, with episodes of cyclical pelvic pain and primary amenorrhea similar to vaginal atresia. Occasionally the patient may consult just for the primary amenorrhea, mainly in low transverse vaginal septum. But they normally settle in the superior third of the vagina (46%) or in the middle third (40%).

The diagnosis can be done with the clinical examination and with a colpohysterosalpingography to retrogradely fill the superior vagina and the uterus in the cases of incomplete septum; and with the bimanual exam to detect pelvic masses corresponding to hematocolpos and eventual hematometra, hematosalpinx and/or endometriosis, as well as with the ultrasound, laparoscopy (normal uterus and adnexs above the great retro-supravesical swelling) and eventually the MRI, in cases of complete transverse vaginal septum. Since there can be other associated urinary and gastrointestinal anomalies, the i.v. urography, the cystoscopy and the opaque enema are also convenient. The differential diagnosis must be reached mainly with the segmentary vaginal atresia, which can actually be included in the same group of anomalies, and with the imperforate hymen. Fig. (23) shows a case we saw with transverse vaginal septum, or more likely with segmentary vaginal atresia, which had previously been tunnelled in a different hospital, but which had again been closed, originating very severe dysmenorrheas after extended spottings. By ultrasound, we could observed the communicating superior hematocolpos and the hematocervix.

- The group of **agensis or hypoplasias** of the ASRM classification (class I) also includes many cases of complex genital malformation. As already stated, for a proper diagnosis, previous to any therapeutic measure, it is probably necessary to resort to the abdominal and transvaginal ultrasound examination, to laparoscopy with laparoscopic puncture of the uterine body and retrograde chromeperturbation or dye injection for HSG, and to the pelvic MRI. The performance of i.v. urography and karyotype is convenient. In the differential diagnosis it is important to discard certain processes such as the adhesion of the labia minora, the labioscrotal fusion of the adrenogenital syndrome, the imperforate hymen, the testicular feminization syndrome (Morris syndrome) or the transverse vaginal septum. The aforementioned diagnostic procedures clarify the diagnosis. And, once the anomalies of the inferior tract and the Morris syndrome are discarded, the major problem may come from the transverse vaginal septum, which can present similar symptomatology and findings to anomalies in the class Ia. Most likely, many cases of complete transverse vaginal septum have been wrongly diagnosed as vaginal agensis. At first, the presence of hematocolpos suggests a transverse septum. Most of these septa affect the superior and middle third, with present inferior vagina, but there may be several septa. And in the cases of vaginal agensis there is no hematocolpos, as it is not of a minimal superior portion. The final diagnosis is frequently given during the performance of the surgery.

We have already commented a case with complete cervico-vaginal atresia, and the cases of cervical agensis in the presence of a functioning endometrial cavity and normal vagina are extremely rare. The symptoms are similar to those anomalies in class Ia, and occasionally only the primary amenorrhea and the infertility have been the reasons for consultation. Naturally, if there is a functioning endometrial cavity, the problem is the great cyclical

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**Figure 22.** Crossed renal ectopia and bicornuate uterus. A, Urography. B, HSG image: transitional bicornuate-subseptate uterus and bilateral hydrosalpinx.
dysmenorrhea and cryptomenorrhea. The vagina can be normal in its depth and width, ending in a blind bag, without a visible cervix or with a rudimentary one. At vaginal and/or rectal examination, a cervical fibrous cord and normal uterine body or pelvic mass due to hematometra, hematosalpinx and/or endometriosis can be felt. The diagnosis is likewise reached with ultrasound, laparoscopy and/or MRI. In some of our cases, cervical atresia was observed in one of the hemicervices corresponding to bicornis-bicollis or didelphys uterus, and it was always associated with an absent or atretic blind hemivagina and, therefore, with ipsilateral renal agenesis. In the first case (bicornis-bicollis) there were, at the same time, communicating uteri and therefore there was no obstructive pathology. In the case of a didelphys uterus however, the cervical atresia generated a great hematometra in the corresponding hemiuterus, hematosalpinx and endometriosis. The right hemihysterectomy solved the problem. Recently, though, we have seen another patient with a present inferior vagina but with a didelphys uterus, atretic in the left side and cavitated and functioning in the right side. It is actually a Rokitansky syndrome with a functioning right uterine horn and present inferior vagina. In another hospital, the patient was being performed cyclical abdominal ultrasound guided punctures of the hematometra (after right adnexectomy due to endometriomas), but we have performed an opening and connection of the functioning hemiuterus into the permeable vaginal fundus and, so far, it is working with normal menstruations.

The most frequent type of agenesis is certainly the Rokitansky-Kuster-Hauser syndrome, which has already been explained, but we must bear in mind its complexity in case there is a small functioning endometrial cavity that then causes retrograde menstruation and endometriosis [106,213]. In other cases with a bigger uterine cavity, as the one above mentioned, the patient could even achieve a posterior pregnancy after the appropriate surgical correction.

- Among the cases of unicornuate uterus (class II in the ASRM classification), those with a cavitated and non-communicating rudimentary horn (IIb) can cause important problems and be complex malformations. They will present retrograde menstruation (or hematometra if the tube was atretic or if a tubal ligation was performed for sterilization) [214-216]; and if the cavitated rudimentary horn corresponded to an atretic hemicervix, there would also be renal agenesis, as already stated. Sometimes they are found as a complication [217] and pregnancy may occur in the non-communicating accessory uterine horn [218] or in the tube of the rudimentary uterine horn [219].

- Finally, some patients may present several associated anomalies of mesonephric, müllerian and/or cloacal origin, originating very complex malformations difficult to be treated [198]. According to our experience, the malformations that have generated more clinical problems, as well as more problems of differential diagnosis and treatment, are the cases of atretic blind hemivagina where the hemicervix of the same side is atretic, with double but non-communicating uteri and with functioning endometrium in both sides; and also those cases that combine mesonephric, müllerian and cloacal anomalies, which will be explained in the study of our material.

General analysis of our patients with genitourinary malformations, Obstetric and gynecologic related pathology.

We have revised and analyzed 561 cases of patients with genital malformations, but some complex cases were referred to us from other Hospitals, so the proportion of complex cases shown in tables does not correspond to our hospital. In 23 cases (4.1%) the uterus was normal, but the patients presented vaginal anomaly (longitudinal or transverse septum, segmentary atresias, etc) or other anomalies, without uterine malformation; and in 538 cases (96%) there was some uterine anomaly, from patients with hypoplasia/agenesis (class I) to DES syndrome/T-shaped, hypoplastic uterus (ASRM class VII).

In Table 1 the distribution of the genital malformations studied is shown, and they are grouped according to the ASRM classification of müllerian anomalies and according to our own embryological classification. Likewise, cases of complex genital malformation and those cases with unilateral renal agenesis (including those with dysplastic kidney and ectopic ureter opening into a blind vagina) as well as their frequency among the different types of genital or genitourinary malformation are given. As it can be seen, the most frequent uterine anomalies were the arcuate uterus (127 cases) and the bicornate-unicollis uterus in another 128 cases (23.8% of uterine anomalies). Complex malformations were observed mainly in the group of agenesis/hypoplasias and among important fusion defects (bicornis-bicollis and didelphys uterus). Unilateral renal agenesis was observed mainly among these fusion defects and in unicornuate uterus cases. More than 50% of our patients with bicornis-bicollis or didelphys uterus had unilateral renal agenesis, while such renal agenesis was exceptionally observed among the anomalies due to defects of reabsorption of the interductal müllerian septum (septate uterus). From the point of view of the embryological classification, we must observe how most complex cases and those with unilateral renal agenesis are included in group 1 (agenesis of all the derivatives of the urogenital ridge, where ipsilateral renal agenesis is observed, though actually they are cases with just one unicornuate uterus and not too complex) and in group 2 (mesonephric anomalies, being these, on the other hand, the most complex cases), but naturally as well among the malformative combinations that include the mesonephric or wolfian anomalies. In all cases, the malformation had been previously researched by studying the medical-surgical records and clinical data, the physical examination, the abdominal and/or transvaginal ultrasound, HSG, i.v. urography and CAT, MRI, laparoscopy, laparotomy and histopathological studies in the appropriate cases. In all cases, the physical examination, ultrasound, HSG and, frequently, i.v. urography and laparoscopy are performed as a basic study. Among the patients with urinary anomalies, 104 cases presenting any pyelocalicial anomaly, renal ptosis, pelvic kidney, horseshoe kidney and all cases with renal agenesis or renal hypoplasia/dysplasia with ectopic ureter have been included. Except for the cases with renal agenesis or renal dysplasia/ectopic ureter, the other anomalies do not bear much relation to genital malformations. In the complex malformations group (97 cases) we have included the above
Table 1. Distribution of all studied genito-urinary malformations, including complex cases and those with unilateral renal agenesis, according to the ASRM classification and to our embryological-clinical classification.

<table>
<thead>
<tr>
<th>Malformations</th>
<th>Not and Seen</th>
<th>Complex malformations (total of malformations)</th>
<th>Unilateral renal agenesis (URA)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% of total</td>
<td>% of total</td>
<td>% of total</td>
</tr>
<tr>
<td></td>
<td>number</td>
<td>number</td>
<td>number</td>
</tr>
</tbody>
</table>

Table 2. Obstetric antecedents in the studied genito-urinary malformations.

<table>
<thead>
<tr>
<th>Malformations</th>
<th>Cases with pregnancy</th>
<th>With newborns</th>
<th>Miscarriages/PM</th>
<th>Miscarriages/PM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
</tbody>
</table>

Table 3. Gynecologic pathologies and other ones associated with genital malformations.

<table>
<thead>
<tr>
<th>Malformations</th>
<th>N (%)</th>
<th>Myomatas</th>
<th>Endometriosis</th>
<th>Uterine</th>
<th>Skeletal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(%)</td>
<td>(%)</td>
<td>(%)</td>
<td>(%)</td>
<td>(%)</td>
</tr>
</tbody>
</table>

reproductive loss, versus only 31.5% in women with uterine anomalies. Among these, the best results were observed, with significant differences, in the cases of the most severe fusion defects and in the unicornuate uterus; and the highest percentage of cases with any living fetus (normal miscarriage and/or perinatal death) occurred in the arcuate, bicorne-unicollis, septate and DES syndrome/hypoplastic T-shaped uterus. Among the patients who got pregnant, 68.6% had reproductive losses in the uterine anomalies group, 25% of those being late losses. In 71% of the patients, there was a perinatal obstetric pathology (breech, prematurity, perinatal mortality). These results are of course similar to what we communicated in previous papers [2,125,220-222]. Heinonen [223,224] has also reported good results achieved in the didelphys uterus. Other authors [225], however, have observed results very different from ours when analyzing the reproductive impact of congenital Müllerian anomalies: “the reproductive performance of the unicornuate and didelphys uteri was poor, while the septate and bicorne uteri was better than expected. The arcuate uterus had no impact on reproduction”. And those results observed by Coll et al [226] differ from both Raga et al [225] and ours as they saw worse results in the septate uterus. All these studies were performed in Spain, so it is evident that there must exist methodological differences in the analysis and cataloging of uterine malformations.

With regard to the gynecologic pathology, Table 2 shows the obstetric antecedents of the studied malformations. Naturally, the perinatal outcome depended upon the class of uterine anomaly and, therefore, those cases with a normal uterus had 71.4% of pregnancies with newborns and absence of any other pregnancy with reproductive loss, versus only 31.5% in women with uterine anomalies. Among these, the best results were observed, with significant differences, in the cases of the most severe fusion defects and in the unicornuate uterus; and the highest percentage of cases with any living fetus (normal miscarriage and/or perinatal death) occurred in the arcuate, bicorne-unicollis, septate and DES syndrome/hypoplastic T-shaped uterus. Among the patients who got pregnant, 68.6% had reproductive losses in the uterine anomalies group, 25% of those being late losses. In 71% of the patients, there was a perinatal obstetric pathology (breech, prematurity, perinatal mortality). These results are of course similar to what we communicated in previous papers [2,125,220-222]. Heinonen [223,224] has also reported good results achieved in the didelphys uterus. Other authors [225], however, have observed results very different from ours when analyzing the reproductive impact of congenital Müllerian anomalies: “the reproductive performance of the unicornuate and didelphys uteri was poor, while the septate and bicorne uteri was better than expected. The arcuate uterus had no impact on reproduction”. And those results observed by Coll et al [226] differ from both Raga et al [225] and ours as they saw worse results in the septate uterus. All these studies were performed in Spain, so it is evident that there must exist methodological differences in the analysis and cataloging of uterine malformations.

With respect to the gynecological pathology (see Table 3), we must underline a higher incidence of leiomyomas among all women with uterine anomaly, a higher frequency of urinary pathology among the cases with bicornuate-bicollis and didelphys-unicollis, and the skeletal anomalies in the group of hypoplasias/agenesis and in the unicornuate uterus, generally with unilateral renal agenesis (group I); this is found in the complex cases we are going to see now.

Complex malformations. Most interesting cases and related pathology.

We will analyze separately our complex malformation cases and show a representative case report of each one of the types considered in our embryological-clinical classification.
1. **Agenesis or hypoplasia of all the urogenital ridge.** Fig. (24) shows the urographic imaging (left renal agenesis) and the laparoscopic findings with a clear absence of the **adnex** (tube and ovary) on the left side and right unicornuate uterus.

**Figure 24.** Agenesis of all the derivatives of the left urogenital ridge. A, Urography showing the left renal agenesis. B, Laparoscopic image showing the right adnex. C, Laparoscopic image showing the absence of left adnex.

2. **Mesonephric anomalies.**

   A) With unilateral hematocolpos. Figure 9A shows the colpo and hysterographic imaging after puncture and injection of a contrast agent in the right blind vagina with hematocolpos. The uterus is bicornuate with communication at an istmic level and spillage of the contrast agent towards the permeable vagina. The malformation diagram is shown in B.

   B) With Gartner pseudocyst. Figure 18C shows the imaging of a HSG performed on a patient with communicating uteri and left cervix permeable towards the left bag or Gartner pseudocyst. A small duct suggesting the remnant of the ectopic ureter or mesonephric duct can be observed on the left. In figure 18B the diagram of the genital tract of another patient with atretic left hemicervix is shown. The HSG here suggested normal bicornuate-unicollis uterus.

   C) With partial reabsorption of the septum. Figure 17 shows MRI showing didelphys uterus and leiomyoma on the right horn and the general diagram of the malformation with partial reabsorption of the septum, didelphys uterus and right renal agenesis. This patient had undergone different surgical operations; reimplantation of the ureter at one year of age, abdominal myomectomy at 22 and later she had a pregnancy in the left hemiuterus with severe gestational complications, especially those derived from the varicocele on that uterine wall, with spontaneous rupture of blood vessels and hemoperitoneum.

   D) Unilateral cervico-vaginal atresia without communicating uteri. The case in figure 20 corresponds to an 18-year old patient, with strong dysmenorrhea. She had been seen and operated on (right adnexectomy due to endometriomas) in a different city and also diagnosed of bicornuate uterus during laparotomy. Intra and postmenstrual dysmenorrheas increased after operation, and she consulted our Emergency Unit for such pain while on holiday. After the transvaginal echographical suspicion of hematometra in the right uterine horn and the finding of ipsilateral renal agenesis, a diagnosis of the type of malformation was given and later confirmed in the posterior laparotomy in which a right hemihysterectomy was carried out. It was very interesting that the right atretic hemicervix ended in another duct that we interpreted as a mesonephric one and right atretic vagina.

   E) Unilateral cervico-vaginal atresia with communicating uteri. Fig. (25) shows the HSG and urographic images and the general diagram of the malformation in a patient with communicating bicornuate uterus and cervicovaginal atresia on the left side.

3. **Müllerian anomalies.**

   A) Affecting the Müllerd ducts. Figure 13 shows the diagram of the genital anomaly of a patient with cavitated and non-communicating uterine horn that did not cause any trouble until a tubal sterilization was done.

   B) Affecting the Müller tubercle. Figure 8C and 9B show the MRI and the laparoscopic HSG image showing complete cervicovaginal atresia. Fig. (26) shows the last surgery when a new opening of the uterus into the neovagina was done. This patient got pregnant spontaneously afterwards and has already given birth (caesarean section).

C) Both. Fig. (27) corresponds to a patient with Rokitansky syndrome and right renal agenesis to whom we did a neovagina according to McIndoe technique. The same dissection and tissue separation evidenced the appearance of “right vaginal fundus”.

4. Combinations.
The case shown in Fig. (28) combined mesonephric, müllerian and cloacal anomalies. A 37-year old patient, single, obese and suffering hirsutism, showed strong dysmenorrheas lasting 10-12 days for which she took contraceptives for 7-8 years with no evident improvement. She has not had sexual intercourse. She refers that when she was born she had a cloacal anomaly for which she had surgery at 8 days of age but has always had a certain feces incontinence. At 12 she had painful abdominal-hypogastric severe symptomatology and after several medical consultations, she underwent surgery with the diagnosis of “vaginal occlusion and priohematometra”. According to the sheet operation report, a “vaginal tunnelling and uterine evacuation” was performed, though she presents a scar of middle, infra and supraumbilical laparotomy. The i.v urography and other tests had proved the existence of right renal agenesis. The pelvic pain and discomfort are permanent but they intensify during menstruation, which lasts too long though she has been taking oral contraceptives for years to relieve the dysmenorrhea.

The physical examination showed a basically normal vulva and anus, with a scar of the cloacal correction. The vagina presents stenosis at 1 cm and it is not permeable for a finger. The ultrasound did not provide well-defined images, but the uterus seemed bicornuate or didelphys, the right side properly developed. An MRI was performed showing unicorinate uterus, without clear visualization of the vagina. With a Foley catheter introduced through the vaginal stenosis, we managed to fill the unicorinate uterus with normal horn shown in the image. Due to the inverted position of the radiographic identification, it was then diagnosed as a left unicorinate uterus. The patient asked for surgery and for her symptoms to be solved. Therefore, a hysterectomy was eventually done since she stated her wish nor did she foresee the possibility of having any children. Finally, in December of 2000, a laparotomy was performed and we observed: non-cavitated rudimentary left hemiuterus with normal tube and ovary as usual in the Rokitansky syndrome, and on the right side, well-developed unicorinate uterus, with normal appearance and normal tube and ovary. A total hysterectomy of both hemiuteri was done, being observed that the right hemicervix ended into a small vaginal cavity, almost occluded in its middle third, as if it was a transverse vaginal septum. The final diagram of the malformation is shown in figure 28F. It is clear that the right side would correspond to a renal agenesis and ipsilateral blind vagina syndrome (the vaginal stenosis must correspond to the opening of the blind vagina she was performed on in the surgery she underwent at 12); and the left side would be the characteristic one in a unilateral Rokitansky syndrome, with normal tube, ovary and left kidney. But besides, as mentioned before, this woman was born with a cloacal anomaly, so her complex malformation consisted on a mesonephric, müllerian and urogenital sinus anomaly. After surgery, the patient progresses normally and suffers no symptoms or discomfort.

The case shown in Fig. (29) presented right unicorinate uterus with atretic left hemiuterus, atretic left blind vagina and also transverse vaginal septum. As in the case in figure 28, she suffered from important pain and pelvic inflammatory disease needing laparohysterectomy.

- As we have already mentioned in the previous section, 97 complex cases are included in our material. In 93 (95.8%) there was a different non-uterine malformation, versus
90/464 (19.4%) in the remaining genital malformations (chi² p<0.0001). Table 4 shows the obstetrical history of these complex malformations: 58% had newborns with no miscarriages or perinatal mortality (PM) and 18.7% had miscarriages or PM and newborns, versus 28.9% and 35.1% respectively in the remaining malformations, the differences being statistically significant (p<0.01). Then, obstetrical problems in complex malformations are fewer than in the remaining genital malformations. And it occurs similarly with regard to the cases of renal agenesis, with even better obstetrical outcome (see Table 5).

There were also significantly less infertility, less reproductive losses on the whole and less late reproductive losses among complex malformations (see Table 6). Late obstetrical pathology (breech, prematurity, PM) was also significantly lower among complex malformations (50% versus 73.2% in the rest of malformations). And the results in renal agenesis cases were similar or better with respect to infertility, reproductive losses and late obstetrical pathology. The gynecological pathology, however, was higher in complex malformations than in the remaining genital malformations, with no differences between right or left renal agenesis, the latter being less frequent.

Table 4. Obstetric antecedents in complex genito-urinary malformations.

<table>
<thead>
<tr>
<th>Malformations</th>
<th>Cases with pregnancy</th>
<th>With newborns N (%)</th>
<th>Miscarriages/PM %</th>
<th>Miscarriages/PM N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>With normal uterus</td>
<td>0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Hydrometrocolpos</td>
<td>0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Acute uterus</td>
<td>0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Bicornis-tunicus uterus</td>
<td>6</td>
<td>2(40.0)</td>
<td>3(50.0)</td>
<td>1(40.0)</td>
</tr>
<tr>
<td>Bicornis-bicornis uterus</td>
<td>10</td>
<td>6(60.0)</td>
<td>1(10.0)</td>
<td>3(30.0)</td>
</tr>
<tr>
<td>Tiedl sphincter uterus</td>
<td>0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Unicollus uterus</td>
<td>10</td>
<td>7(70.0)</td>
<td>2(20.0)</td>
<td>1(10.0)</td>
</tr>
<tr>
<td>Subtracted uterus</td>
<td>0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Septate uterus</td>
<td>6</td>
<td>3(50.0)</td>
<td>0.0</td>
<td>3(50.0)</td>
</tr>
<tr>
<td>DES Syndrome, T uterus</td>
<td>0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Total of complex cases</td>
<td>32</td>
<td>18(56.2)*</td>
<td>6(18.7)</td>
<td>8(25.0)</td>
</tr>
</tbody>
</table>

Table 5. Obstetrical antecedents in the malformations with unilateral renal agenesis.

<table>
<thead>
<tr>
<th>Malformations</th>
<th>Cases with pregnancy</th>
<th>With newborns N (%)</th>
<th>Miscarriages/PM %</th>
<th>Miscarriages/PM N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>With normal uterus</td>
<td>0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Hydrometrocolpos</td>
<td>0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Acute uterus</td>
<td>0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Bicornis-tunicus uterus</td>
<td>3</td>
<td>1(33.3)</td>
<td>1(33.3)</td>
<td>1(33.3)</td>
</tr>
<tr>
<td>Bicornis-bicornis uterus</td>
<td>10</td>
<td>6(60.0)</td>
<td>1(10.0)</td>
<td>3(30.0)</td>
</tr>
<tr>
<td>Tiedl sphincter uterus</td>
<td>0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Unicollus uterus</td>
<td>9</td>
<td>7(77.8)</td>
<td>1(11.1)</td>
<td>1(11.1)</td>
</tr>
<tr>
<td>Subtracted uterus</td>
<td>0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Septate uterus</td>
<td>0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>DES Syndrome, T uterus</td>
<td>0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Total of cases</td>
<td>32</td>
<td>18(56.2)*</td>
<td>6(18.7)</td>
<td>8(25.0)</td>
</tr>
</tbody>
</table>

Table 6. Infertility and recurrent miscarriage in patients with complex genital malformations.

<table>
<thead>
<tr>
<th>Genital Malformations (N)</th>
<th>Infertility (l. 10 years) (%)</th>
<th>Cases with pregnancy with antepartum PM %</th>
<th>Total of patients with antepartum PM %</th>
<th>Patients with late reproduction losses %</th>
<th>Patients with late reproduction losses N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>With normal uterus</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Hydrometrocolpos</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Acute uterus</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Bicornis-tunicus uterus</td>
<td>10.0</td>
<td>10.0</td>
<td>10.0</td>
<td>10.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Bicornis-bicornis uterus</td>
<td>10.0</td>
<td>10.0</td>
<td>10.0</td>
<td>10.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Tiedl sphincter uterus</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Unicollus uterus</td>
<td>10.0</td>
<td>10.0</td>
<td>10.0</td>
<td>10.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Subtracted uterus</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Septate uterus</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>DES Syndrome, T uterus</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>TOTAL (%)</td>
<td>10.0</td>
<td>10.0</td>
<td>10.0</td>
<td>10.0</td>
<td>10.0</td>
</tr>
</tbody>
</table>

In some complex malformation cases several really outstanding obstetric and gynecological problems occur. Fig. (30) shows the hemiuteri of the patient mentioned in figure 17 after a caesarean section. The gestation had taken place in the left hemiuterus. Apart from the previous problems of this patient she consulted at the Emergency unit in the 30th week of gestation for strong abdominal pain, hypotension and sickness suggesting uterine rupture. The abdominal ultrasound and CAT showed hemoperitoneum. Though expectant management was followed at first, a laparotomy and caesarean section were later necessary.
Table 8. Presence of any gynecologic pathology in the patients with renal agenesis.

<table>
<thead>
<tr>
<th>Malformations</th>
<th>N° of cases</th>
<th>Gynecologic pathology related to malformations N° (p*)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>RRA</td>
</tr>
<tr>
<td>With normal uterus</td>
<td>1</td>
<td>(1)</td>
</tr>
<tr>
<td>Hypoplasia/agenesis</td>
<td>3</td>
<td>(2)</td>
</tr>
<tr>
<td>Acute uterus</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Bicornical-unicollis uterus</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Bicornical-bicornicis uterus</td>
<td>25</td>
<td>14</td>
</tr>
<tr>
<td>Difurcatus uterus</td>
<td>18</td>
<td>4</td>
</tr>
<tr>
<td>Unicollis uterus</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Sub-epigastric uterus</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Splenocele uterus</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>DES Syndrome/T-uterus</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td><strong>Total of malformations</strong></td>
<td>58</td>
<td>22</td>
</tr>
<tr>
<td>Remaining</td>
<td>563</td>
<td>228</td>
</tr>
</tbody>
</table>

Physiopathological and etiopathogenical deductions from the study of our complex malformation cases.

In part, they have already been explained in previous sections, so here we will only add some interesting aspects. Our material includes a detailed study of 58 patients with unilateral renal agenesis (though at the time of writing this paper we had studied 61). In our opinion it is the biggest series ever published in the literature, and this and all the other published papers where the genitourinary tract has been properly studied [48-54,133-151] confirm the hypothesis we proposed some years ago [3,6,7,9,56,57,227,228]: the unilateral renal agenesis is systematically associated: 1) with agenesis of all the derivatives of the urogenital ridge of that same side (group... of our embryological-clinical classification), or 2) with ipsilateral atretic or blind hemivagina or cervico-vaginal atresia with uterine anomaly (fusion or reabsorption müllerian defect). In some cases, as already seen, there is partial reabsorption of the intervascular septum. This systematic association and the previous experimental studies by Marshal and Beisel [15] and Boks and Drews [16] were the basis for our suggestion that the vagina derives embryologically from the Wolff ducts and the Müller tubercle [3,7,56], a hypothesis that we have later reasserted in different publications [6] and with new experimental studies [39].

Among the 58 cases studied with unilateral renal agenesis, there were 7 in which there actually was severe renal hypoplasia and even complete absence, but with an ectopic ureter opening into an ipsilateral blind vagina. These cases are as shown in figure 21 or the one shown in Fig. (31) and they equally reassert the mesonephric origin of the vagina. It has also been mentioned that the ureteral bud originates in the mesonephric duct, right from its opening into the urogenital sinus, and then, going to the metanephros, forms the definitive kidney there. The lesion or injury of one of these Wolffian or mesonephric ducts with lack of contact with and/or opening in the urogenital sinus will produce the blind vagina and the absence of ureteral bud formation, with the consequent renal agenesis. However, the ectopic exit of the ureteral bud, higher in the mesonephric duct, will cause cases of renal hypoplasia (the farther from the normal spot the ureteral bud has sprouted, the more dysplastic the kidney will be [38]), the possible opening of the ectopic ureter into a permeable or blind vagina, and also the uterine anomalies by the inducing role of the Wolffian ducts over the Müller ducts in the formation of the uterus [37,44,56,229,230]. Bremond et al [231] stated the hypothesis of the Wolffian diverticile in which the Müller duct, the Gartner cyst and the ureter will open. It could also be that there are different atretic ectopic ureters coming from a common mesonephric duct [232]. These cases could be due to an ectopic sprout of additional

There were big varicosities above the gestational left hemiuterus, whose rupture and tears had caused the hemoperitoneum. The photograph was taken after the caesarean section and the corresponding aspiration and hemostasis.

Figure 30. Photography taken after caesarean section on the patient with the malformation shown in Figure 17. Gestation in the left hemiuterus with severe complications during pregnancy (see text). Observe the varicosities that still persist above that left hemiuterus.

Figure 31. Diagram of the genito-urinary malformation of patient with single ectopic ureter opening into left blind hemivagina, with left renal dysplasia and associated utero-vaginal duplication (from Acién et al, Int J Gynecol Obstet 1990;31:179-185).
ureteral buds high in the mesonephric duct, which in some cases would cause ureteral duplicity with the ectopic branch ending in the vesical neck, urethra or vaginal vestibule [233,234].

Certainly, cases of ectopic ureter opening into supposed Gartner cysts with ipsilateral renal hypoplasia or dysplasia [189,196], or in hydrocolpos [184], or in duplicated müllerian ducts [198] have been communicated, many times with insufficient surgical solutions or varied embryological interpretations [235-238]. These ducts, though, could actually be mesonephric remnants into which an atretic ectopic ureter can open [239]. Other cases as those recently published by Dwyer and Rosamilia [5] could be in fact vesico-urethral duplications and not a real ectopic ureter.

The supposed Gartner cysts and other paravaginal remnants of the wolffian ducts associated with uterine anomalies are really blind hemivaginas (mesonephric duct) and are always associated with unilateral renal agenesis or hypoplasia when there is an atretic ectopic ureter, interpreted in some publications as mesonephric remnant [190], opening into a blind vagina or into the same cervix, via the mesonephric duct [7].

The exceptions to the rule of renal agenesis-blind vagina are the cases of severe agenesis or hypoplasia of all the derivatives of the urogenital ridge afore mentioned and those cases in which a partial reabsorption of the intervaginal septum has occurred. In the latter, the septum does not usually reach the inferior third of the vagina [9,56] and it manifests in the way of a buttonhole on the anterolateral wall of the permeable vagina, giving access to the organs on that side [240].

It can be seen, then, how the analysis of the genital malformations, especially the complex ones, as well as their symptomatology and physiopathology, make us reassert our hypothesis about the embryology of the human vagina as derived from the mesonephric or wolffian ducts together with the Müller tube. Therefore, all the lesions of the mesonephric duct are associated with unilateral renal agenesis and utero-vaginal anomalies. If the injury is distal, blind hemivagina with hematocolpos is observed; if it is higher, a Gartner pseudocyst may be observed in some cases, while in others there is complete vaginal or cervico-vaginal agenesis. And at the same time, both anomalies may be: a) with communicating uteri (apparently there is bicornuate or septate uterus) or b) without communicating uteri, and then retrograde menstruation, endometriosis and unilateral hematometra (if the tube is occluded) are eventually observed.

The Rokitansky syndrome would be, however, an exclusively müllerian anomaly, of the Müller ducts and tube. There is no renal agenesis (and if there is so, the neovagina also seems anomalous as seen in figure 27), and this anomaly (Rokitansky syndrome) may also be unilateral. But there may be mesonephric and müllerian malformative combinations, alternating with respect to the affected side. It could be a müllerian anomaly on one side (unilateral Rokitansky syndrome) and, on the other, a mesonephric anomaly with blind hemivagina and ipsilateral renal agenesis.

Coming back then to the etiopathogenesis of malformations, we believe that the direct cause of the majority of the malformations is not known [6]. However, the pathogenesis of the majority of them can be correctly explained and understood through the embryological hypothesis presented in Acién [3] and other publications by us. In short, the vagina is formed from the Wolffian ducts and the essential participation of the Müller tube. The lesion or alteration of any of these two elements leads to complex malformations that affect all the genitourinary system and in particular, the uterus (failure of the inductor function of the Wolffian ducts) or just the vagina (if the Müllerian tube fails).

Therapeutic management of the female genital tract malformations

It is impossible to outline a single uniform treatment, given the great diversity of situations and possible combinations in the wide chapter of malformations of the female genital tract. When required, the solution will always be surgical, but in the most frequent malformations, it is not generally necessary. And in the rest of malformations the solution is frequently very simple and, what is really essential is a correct diagnosis to avoid inappropriate and/ or unnecessary surgery. We will analyze each type of malformation following the classification stated in the previous sections.

1. Agenesis or hypoplasia of a urogenital ridge: no treatment is needed.

2. Mesonephric anomalies: In the renal agenesis and ipsilateral blind vagina syndrome, after a proper diagnosis, only the removal of the intervaginal septum with the evacuation of the hematocolpos (see figure 16) [241,242] or a wide resection of this wall in the Gartner pseudocyst type [Fig. (32)] may be needed. A laparotomy will be required if there is hematosalpinx and endometriomas, but in general terms, endometriosis disappears when the obstructive anomaly is corrected. It may be necessary as well to extirpate the hemiuterus with atretic cervix or the cavitated non-communicating rudimentary horn [243,244], though Perino et al [245] have done hysteroscopic metroplasty under simultaneous abdominal ultrasound to evacuate and correct a “complete septate uterus with unilateral hematometra”. Afterwards, also Cararach et al [246], Romano et al [247] and others have done this hysteroscopic metroplasty.

![Figure 32. A. Punction of the left blind hemivagina (<<). B. Image obtained while injecting a contrast agent through the previous punction. The left blind vagina (**) and the supposed mesonephric duct (<) are shown. C. Vaginal via: right hemicervix (>>>) and left vaginal fundus after resection of the intervaginal septum (*). D. Hystologic section of the intervaginal septum: squamous (<-) and inflammatory (>>) epithelium.](image-url)
However in the case of uterine duplicity, a hemihysterectomy must be performed. And if there is dysplastic kidney with ectopic ureter opening into the blind vagina, a nephrectomy and ureterectomy will be required. The excretion of the ectopic ureter may also be required if it is associated with ascending infections and related problems, even if there is no detectable renal mass. And surgery at the level of the genital tract depends on the associated anomaly.

3. Müllerian anomalies:

- **Transverse vaginal septum.** The complete transverse septum must have early surgery and, generally, vaginal anastomosis is possible after the evacuation of the superior hematocolpos [248]. The incomplete septum is usually diagnosed later (for dyspaurenia, or at delivery) and a vaginal plastia in Z can be done.

- **Agenesis and hypoplasias (AFS Type I):**
  -- **Vaginal or cervico-vaginal atresia.** If the uterus and/or tubes also present malformations or other alterations, so that the reproductive capacity is low despite successful creation of a neovagina, a hysterectomy is the elective procedure even in young patients. It has been described that when there is also cervical agenesis, every attempt to make the cervix permeable usually fails, patients show serious complications and normal menstruations and posterior pregnancy have been rarely achieved under these conditions [102,249]. However, we have a case in which first we did a neovagina (Mc Indoe technique) and in a second surgery, after partial resection of the cervical portion and permeabilization of the remaining atretic cervix, the latter was opened into and sutured to the superior edge of the previous neovagina, leaving an intrauterine Foley catheter for some days. She had normal menstruations for some years but, later, the remaining cervical portion became stenosed again and new surgery was required. After the resection of all the lower portion of the uterus up to the endometrial cavity and new opening of the uterus into the neovagina, normal menstruations reappeared and, recently she got pregnant spontaneously and has been performed a caesarean section at 36 weeks (see figure 26).

If the uterus and cervix are normal, the surgical correction depends on the atretic vaginal segment. If the distance between the vaginal blind bag and the superior portion of the permeable vagina is short, a vaginal anastomosis can be done as in the transverse vaginal septum. But when trying to do a vaginal anastomosis, if it is done early, we may find many associated technical problems, not only with the surgical technique on the immature genitals, but also with the mobilization of the proximal portion of the vagina. And, in fact, postsurgical vaginal constriction has occurred in some cases despite multiple dilatations, ending finally in hysterectomy [250]. Jeffcoate [251] recommends waiting until an important superior hematocolpos is formed so that it is possible to easily penetrate into the superior portion of the vagina and for an adequate vaginal epithelium lining to exist in order to do the anastomosis. A puncture and aspiration with needle is done to select the spot of the surgical penetration and special attention must be paid to the performance of the transversal incision on the vaginal stenosis, as far as possible from the urethral meatus.

If the atretic segment is bigger, and therefore, the area between both the superior and inferior portions of the vagina is large and fibrous, or the atresia affects all the vagina making the anastomosis impossible, the carrying out of a neovagina must be considered, being preferable the use of inert material prosthesis and skin graft. It must be done early (13-14 years) to avoid endometriosis [252,253]. However, if a hysterectomy is required due to the associated pathology, then the creation of the neovagina must be postponed until the age of 18-20, at which surgery is technically easier, the patient is more mature and it can be followed by sexual intercourse.

-- **Cervical agenesis.** If the vagina is normal, we can try the creation of a fistulous way endometrium-vagina by placing polyethylene or rubber tubes. Some published cases have achieved to keep menstruation but not pregnancies and, in general, hysterectomy is required [102]. Nevertheless, Zarou et al [254] described conception in one patient after the creation of a long fistulous way through a rudimentary cervix after longitudinal incision on the anterior wall of the uterus and placing of small polyethylene tubes sutured to the endometrium. Other authors have used similar techniques, or modifications, or have used a T-shape rubber tube removed after 3 months [255]. But Geary and Weed [256], after serious complications in their cases even with some deceases, noticed that the patients with cervical agenesis (and also those with cervical atresia) must be treated with definitive surgery (this is, hysterectomy). They even suggested that the creation of an artificial duct would allow, more than inhibit, an ascending infection and, besides, the absence of cervical mucus would make conception highly improbable. So, for these reasons, heroic surgical efforts made to preserve fertility would not be justified in most patients, especially if cervical and vaginal agenesis co-exist [250]. But we have formerly described one of our cases of cervico-vaginal atresia operated successfully with respect to menstruations for several years, and with pregnancy and posterior delivery/caesarean section. Certainly, there are already some published cases with successful gestation (spontaneous, IVF or ZIFT) after conservative surgical correction of the cervical atresia (see summary of published cases in Deffarges et al [257]), having been vaginal aplasia associated in 3 of them and in 2 [258,259] after having performed surgery similar to the one we formerly described for our patient (vaginal Mc Indoe operation plus abdominal cervico-uterine resection until endometrial cavity and reimplantation in the neovagina). Deffarges et al [257] have revised a total of 18 cases of utero-vaginal anastomosis in women with cervical or cervico-vaginal atresia, most of them successful with regards to menstruation and gestation, even when there was associated vaginal aplasia (in 7 patients, 2 of whom got pregnant later on). Therefore, they stress that this surgical performance should be done even if there is associated vaginal aplasia and that the diagnosis and surgery should be done early in order to avoid the development of associated pelvic alterations (endometriosis, adherences and pelvic blockade). More recently, we have operated on another case (actually a Rokitansky syndrome previously mentioned). In this patient we have opened, after resection of all the cervical and low corporal uterine portion, the cavitated right uterine horn into the vaginal fundus [Fig. (33)]. She has had normal menstruations for more than three years and is now undergoing ART/IVF treatments in search of gestation.

-- **Corporal or fundic agenesis.** There is no treatment available and usually there is no surgical indication.
Figure 33. Patient with present vagina but with cervical agenesis, didelphys uterus with atretic rudimentary left horn and with cavitated right uterine horn, with hematometra and previous laparotomy and right adnexectomy and then removals of the hematometra by transabdominal echoguided punctures. We did resection of all the right atretic non permeable cervico-uterine portion up to the endometrial cavity (A), and then, we reimplanted it on the vaginal fundus (B). Post-surgery image in C. D, Presurgery transvaginal ultrasound. E, Transvaginal ultrasound 2 months after surgery and after normal menstruations.

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**Tubal agenesis.** If the other tube is normal, no treatment is required. If there is segmentary agenesis, there could be higher ectopic pregnancy risk. Eventually, end-to-end anastomosis or its extirpation may be indicated.

**Combined utero-vaginal agenesis (Mayer-Rokitansky-Kuster-Hauser syndrome).** These patients may require the performance of a vaginoplasty or creation of a neovagina with prosthesis and skin graft (McIndoe technique) [260] [Fig. (34)]. Currently, though, some good results with the covering of the prostheses just with Intercede [261], or also by using the buccal [262] or vesical [263] mucous have been reported.

Figure 34. Vaginoplasty according to McIndoe technique. A. Prosthesis we use in our Obs-Gin Service (own design). B. Covering the prosthesis with Intercede plus skin graft. C. External genitalia of the patient before surgery. D. Dissection of the neovaginal cavity. E. Placed prosthesis.

The dilatation therapy by Frank [264] often excludes the necessity of carrying out a neovaginoplasty with prosthesis by skin grafts. And even in patients who require the McIndoe surgery, the dilatation therapy may be of help, creating a wider vagina and making the surgical treatment easier [265,266]. In fact, in some patients, the attempts of sexual intercourse by themselves are enough to form a satisfactory vagina [267].

Creatsas et al [268] have published the results of 111 patients with Rokitansky syndrome after creating a neovagina by following the Williams method with the Creatsas modification, a simple and effective technique. Moreover, a variation of Frank’s dilatation technique is the Vecchietti operation (with hard prosthesis and traction over the abdominal cavity) and it can also be done via laparoscopy [269-271]. In any case, if there are one or both cavitated rudimentary uterine horns (retrograde menstruation and endometriosis), their laparoscopic or laparotomic extirpation will be required [Fig. (35)].

Another technique to create a neovagina in the Rokitansky syndrome is the sigmoidal neovagina (the creation of which via laparoscopy has been recently proposed). And also by using a perineal flap from the Douglas cul-de-sac [272,273].
But the greatest experience, with a longer posterior observation, is with the surgical creation of a cavity coated with or without epidermic free grafts (McIndoe operation) [260,274]. It is the one we do by using dexon prostheses we designed many years ago (see figure 34) and the risks when using the appropriate technique are scarce.

- **Unicornuate uterus (AFS class II).** It requires no other treatment but the eventual and rare need of cerclage during pregnancy. However, if it is associated with cavitated or functioning rudimentary uterine horn, the extirpation of the latter will be required [275-278]. But the extirpation of a non-functioning rudimentary horn for the treatment of infertility or miscarriages has no basis, though Buttram did it in four patients who had a long history of infertility and all of them got pregnant after 6 months from surgery [250]. Neither do we think as having any basis the hysteroscopic treatment of the cavitated and non-communicating rudimentary horn [279]. Sometimes, however, other different surgical measures, like the myomectomy, are needed, since we think that these patients have uterine leiomyomas more frequently, including rudimentary uterine horn and Rokitansky syndrome cases [280,281].

- **Didelphys uterus (class III).** Since it usually appears with longitudinal vaginal septum, the removal of this septum may be convenient if there is dyspareunia [282], or during laparoscopy and at delivery. It must be done if it is associated to blind hemivagina, but the metroplasty is not indicated nor has any logic. In the cases of blind vagina with hematocolpos we have seen that a wide incision of the intervascular septum and a complete drainage of the hematocolpos are sufficient. But, in general, to avoid a posterior narrowing, it is better to do an excision of the septum as wide as possible, as if it was a longitudinal vaginal septum.

- **Bicornuate uterus (class IV).** If it is the cause of recurrent miscarriage, a Strassmann metroplasty may be required [283-285]. Generally, similar results are achieved only with cervical cerclage in the third month of pregnancy [286], but if miscarriages repeat, a metroplasty must be done [Fig. (36)]. Kirk et al [287] have questioned, though, the efficacy of metroplasties in the treatment of multiple pregnancy losses.

- **Septate uterus (class V).** Likewise, it may require metroplasty (Tompkins technique) if it is the cause of reproductive losses. Currently, a hysteroscopic resection of the septum is recommended [288-292], although a cervical cerclage may also be required (or be enough).

- **Arcuate uterus (class VI).** It may require cerclage, but in general terms, it does not need treatment.

- **DES anomalies (class VII).** Again, they may require cerclage, but in general they do not need treatment. Some authors have recommended hysteroscopic metroplasty, doing lateral incisions to widen the cavity.

4. **Cloacal and urogenital sinus anomalies.** In the imperforate hymen: cross incision of the hymenal membrane, digital enlargement and removal of the hematocolpos. Generally, cloacal anomalies may require complex surgery that will depend on the anomaly and affected organs in each case. In the anomalies of the external genitalia, only minor plastic surgery is required in general.

5. **Combinations and other complex malformations.** Surgery is also usually required [294] and, as mentioned in the case reports previously commented on, it depends on the symptoms, the anomaly and the affected organs, bearing always in mind, as we have stated many times, the embryology and physiopathology.

In general terms, then, surgical techniques in the correction of genital malformations depend on the anomaly, on its complexity, on the patient’s symptoms and on its proper embryological interpretation. It can frequently be solved by vaginal via (or hysteroscopy) but the laparotomy is often needed. The surgical laparoscopy has been successfully used in certain genital malformations, though we should be cautious. We find the attempts to perform Strassmann operation through laparoscopy inappropriate. Pelosi et al [295] have done metroplasty transvaginal via by posterior colpotomy and assisted by laparoscopy, but neither do we believe it to be the most appropriate technique. Other laparoscopic surgical approaches will have to be done as we go along and according to the embryological and physiopathological knowledge of the anomaly.

At the moment, some authors are inclined to the hysteroscopic resection of the uterine septum as soon as it is diagnosed, but others recommend only cerclage if there is cervical incompetence or as a prophylactic method; and metroplasty is done if reproductive losses happen again. But we must never forget that hysteroscopic resection also has posterior problems (uterine rupture in the case of Kerimis et al [296]), and that when the intercervical septum is resected, there is an insufficiency that will have to be corrected with cerclage. Certainly, we have primarily performed cerclage alone and the results concerning deliveries with newborn are of 80% in our material.
These rates are similar to those reported for metroplasty by different investigators, though we believe this surgery must be done if gestational losses reoccur. A laparotomic metroplasty can also be done, but there is the inconvenience of postsurgery pelvic adherences and it is no longer used. In our opinion, except for some specific cases (in the septate or bicornuate uterus cases, approximately 20% of them), abdominal or hysteroscopic metroplasty is not needed and, besides, this procedure does not exclude the necessity to do a cerclage during gestation [220].

Additional comments and clinical recommendations

1. As shown in Table 7, associated endometriosis was more frequent among the complex cases. In some previous publications [106,297,298] we analyzed the association genital malformation-endometriosis (11%) and other authors [299-302] also mention it, but the predisposition of malformations to endometriosis is unclear. Neither the type of genital malformation nor the obstructive pathology in the presence of associated endometriosis nor its severity, evidence a predisposition [298]. Some cases with forced retrograde menstruation from menarche due to an obstructive genital anomaly do not show endometriosis, and when it is observed, this one seems of a different type from the one that usually causes infertility and disappears when the obstruction is corrected [56,303]. The coincidence then of typical endometriosis and genital malformation appears to be merely accidental and the retrograde menstruation (not necessarily abundant), genetic predisposition and, above all, the decrease in the lymphocytotoxic response by alteration of the cellular immunity will play a role.  
2. Since we have included all the renal agenesis cases among the complex malformations, urinary anomalies were also significantly higher in our material. Nevertheless, anomalies such as pyelocalitial duplications, renal ptosis, etc, are frequently found without any genital malformation, 
3. The proper knowledge of the genito-urinary embryology is essential for the understanding, research, diagnosis, and consequently, the adequate treatment of genital malformations, especially the complex ones and those that generate gynecologic problems, above all in young women. The embryology of the vagina is frequently explained as derived from the Müllerian ducts and so, many complex malformations are not properly understood. Our embryological hypothesis of the vagina as derived from the Wolffian ducts together with the Müllerian tubercle does explain all the anomalies and on this basis, we have stated our embryological classification of the genital malformations. The different clinical classifications (ASRM) usually refer only to uterine anomalies and are useful for the assessment of fertility problems, but they do not include all the genital malformations that can originate important gynecological problems. The classification of female genital malformations attending the embryology of the genito-urinary tract is clinically applicable and allows for a better understanding of the complex malformations and their correct resolution [6,304].  
4. With respect to related fertility problems, it must be stated as a synthesis that uterine anomalies are little related to infertility problems, though there is a lower rate of embryonic implantations in IVF [305], but it does clearly relate to recurrent miscarriage. The arcuate and bicornuate uteri are observed in more than 15% of patients with recurrent miscarriage, but it is even more frequent when we include early miscarriages and immature deliveries among the reproductive losses [124]. These findings are also related to cervical incompetence, usually associated with uterine malformations. In other cases of uterine malformation with early recurrent miscarriage, such early reproductive losses are more likely caused by other etiological factors, which could also be associated with the malformation. For example, in the hypoplastic uteri, except for some few cases related to DES syndrome and cervical incompetence, the recurrent miscarriage seems to relate to other causes (immunological, luteal insufficiency, etc), which also seem more frequent in patients with uterine anomalies. Therefore, such factors must always be studied before attributing reproductive losses to a uterine anomaly. And considering the reproductive losses from the analysis of all uterine malformations, it is evident that there is a high incidence of miscarriages among them (more than 50%), but only 17% have recurrent miscarriage. Again, most reproductive losses take place in the bicornuate (and arcuate) uterus, while the septate uterus has a better prognosis (against the criteria of some authors [226,306]) probably due, or at least in part, to differences in cataloging of uterine malformations. In the didelphys and unicornuate uteri, though, the rate of miscarriages is low, and in all groups there is a high rate of breech presentation and immature deliveries.

5. From the gynecological point of view, attention must be paid for a correct diagnosis and therapeutic management of patients, and before starting any surgery, all diagnostic possibilities must be considered. At present, the transvaginal ultrasound and, eventually, the MRI, may be of great help to avoid invasive methods or methods requiring hospital admission, the anaesthesia and the use of the operating theatres with their corresponding expenses, apart from the frequent resistance of the patient to undergo studies if there is no symptomatology or if she does not wish any more pregnancies. Now, if the laparoscopy is advisable it must be done; exceptionally, a laparotomy would be required, but in any case it would be done with a therapeutic intention. Most obstructive anomalies (but not all of them, nor exclusively) can originate endometriosis by forced retrograde menstruation. We have checked, though, the common disappearance of the endometriosis when the genital anomaly is corrected.

6. Clinical recommendations:
A) Before any suspicion of genital malformation, kidney and urinary vias must be studied (ultrasound, i.e. pyelography, and eventually cystoscopy and cystography). And every time there is renal agenesis, a genital
malformation must be searched for, since there must be agenesis or hypoplasia of all the derivatives of the ipsilateral urogenital ridge, or blind (or imperforate), atretic vagina or vagina with hematocolpos and, normally, müllarian duplicity.

B) A HSG must be systematically performed and as well we have to pay attention, before unicornuate uterus, to the fact that there may be another hemiuterus on the contralateral side whose cervix has not been observed, or there may be a cavitated rudimentary uterine horn. The ultrasound and other means of study help the diagnosis, but they do not exclude nor are as efficient as the HSG.

C) Before primary amenorrhea with normal phenotypical sexual development, and the presence of an imperforate hymen excluded, we must think of the genital agenesis group. An early diagnostic explanation is especially important if there is cyclical pelvic pain. But this may not exist (in the transverse vaginal septum, for instance) even in the presence of a great hematocolpos.

D) Intense cyclical pelvic pain, or marked intramenstrual dysmenorrhea, should make us think of and search for the possible presence of non-communicating cavitated uterine horns, or of unilateral cervical atresia.

E) Before fertility problems (recurrent miscarriages, late miscarriages or immature or premature deliveries) as well as repeated breach presentations or transversal situations, a uterine anomaly should always be excluded by doing a HSG.

F) The müllarian anomalies (ASRM class from II to VII) usually present fertility problems, but by themselves, very rarely do they cause gynecological problems. In any case, the surgical correction is seldom needed. But attention must be paid to the performance of a tubal sterilization in case of bicornuate uterus with no previous HSG: we might be closing the tube that drains a functioning cavitated rudimentary horn and then an severe intra and postmenstrual dysmenorrhea would start.

G) The gynecologist must be on the alert for the clinical features referred (intra and postmenstrual dysmenorrhea, cyclical pelvic pain, etc) by young people, but also and especially to:
- Metrorrhagia or postmenstrual spotting lasting some days.
- Metrorrhagia or malodorous postmenstrual spotting.
- Incontinence or permanent urinary loss in between normal micturitions.
- Pelvic masses, endometriosis (most of the endometriosis diagnosed in young women under 18-20 frequently have their origin in an obstructive genital anomaly) and supposed metroadnexitis in teenagers.
- Low pelvic mass or paravaginal cysts found along the right or left antero-lateral wall of the vagina.
- Supposed Gartner cysts with the same location on the antero-lateral vaginal fundus.

In all these situations there can exist a complex genital or genito-urinary malformation, whose surgical resolution, at least symptomatically, is usually though, easy to do.

Conclusions

1. The obstetric and gynecological pathology is increased in all the female genital malformations, but especially the obstetric pathology in the bicornuate uterus and the gynecological pathology in the complex malformations. Their correction is many times necessary from the point of view of the fertility when there are recurrent miscarriages and it is essential to solve the symptoms of many complex malformations.

2. Complex malformations present diagnostic-therapeutic problems, especially those due to anomalies of the mesonephric ducts and malformative combinations.

3. Before deciding any surgery when suspecting a female genital malformation, we must think of the embryological aspects and use the diagnostic procedures and the necessary therapeutic orientation, always according to the previous scientific approach, adaptable to each specific case.

4. Renal agenesis is systematically associated with ipsilateral blind hemivagina with hematocolpos, or with partial reabsorption of the interovaginal septum. But if the lesion of the mesonephric duct occurs at a higher level, not so distally, such renal agenesis is associated with a Gartner pseudocyst and, occasionally, with complete ipsilateral cervico-vaginal atresia.

5. Inversely, the presence of unilateral blind vagina with hematocolpos or the also unilateral atresia with hematometra and similar alterations, are systematically associated with ipsilateral renal agenesis.

6. Some published cases with ectopic ureter in Gartner cyst actually correspond to: 1) atretic blind hemivagina, or 2) cloacal anterior anomaly with bladder and urethra duplication.

7. The cases studied and those published in literature support the embryological hypothesis of the human vagina as coming from the mesonephric or wolffian ducts together with the Müllerian tubercle.

8. The proposed embryological-clinical classification of genital or genito-urinary malformations is appropriate to all malformations and to suggest their origin and eventual correction, the most complex cases especially included.

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