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The history of female genital tract malformation classifications and proposal of an updated system†

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BACKGROUND: A correct classification of malformations of the female genital tract is essential to prevent unnecessary and inadequate surgical operations and to compare reproductive results. An ideal classification system should be based on aetiopathogenesis and should suggest the appropriate therapeutic strategy.

METHODS: We conducted a systematic review of relevant articles found in PubMed, Scopus, Scirus and ISI webknowledge, and analysis of historical collections of 'female genital malformations' and 'classifications'. Of 124 full-text articles assessed for eligibility, 64 were included because they contained original general, partial or modified classifications.

RESULTS: All the existing classifications were analysed and grouped. The unification of terms and concepts was also analysed. Traditionally, malformations of the female genital tract have been catalogued and classified as Müllerian malformations due to agenesis, lack of fusion, the absence of resorption and lack of posterior development of the Müllerian ducts. The American Fertility Society classification of the late 1980s included seven basic groups of malformations also considering the Müllerian development and the relationship of the malformations to fertility. Other classifications are based on different aspects: functional, defects in vertical fusion, embryological or anatomical (Vagina, Cervix, Uterus, Adnex and Associated Malformation: VCUAM classification). However, an embryological-clinical classification system seems to be the most appropriate.

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CONCLUSIONS: Accepting the need for a new classification system of genitourinary malformations that considers the experience gained from the application of the current classification systems, the aetiopathogenesis and that also suggests the appropriate treatment, we proposed an update of our embryological–clinical classification as a new system with six groups of female genitourinary anomalies.

Key words: female genital tract malformations / uterine malformations / Müllerian anomalies / embryology / genito-urinary malformations

Introduction

The complex topic of female genital tract malformations should include malformations that affect the development and morphology of the Fallopian tubes, uterus, vagina and vulva, with or without associated ovarian, urinary, skeletal or other organ malformations; the topic should exclude the abnormalities of sexual determination [involving chromosomal alteration, male histocompatibility (HY) antigen, sex-determining region of the Y chromosome (SRY) and testis-determining factor (TDF) gene or the gonads] and sexual differentiation (by abnormal steroidogenesis or pseudohermaphroditisms). Most of the female genital tract malformations affect the uterus, and therefore, they are often referred to as uterine or Müllerian (paramesonephric) malformations. However, many of the anomalies that affect the Müllerian ducts could originate as a mesonephric (Wolffian) anomaly or in the female gubernaculum.

Female genital tract malformations are frequent but are not always detected. Therefore, their true prevalence in the general population is unknown because many are asymptomatic and not noticed (Acién *et al*., 2004a), which may create methodological bias (Grimbizis *et al*., 2001; Troiano and McCarthy, 2004; Saravelos *et al*., 2008). However, the current availability of a wide range of non-invasive diagnostic procedures provides the opportunity to detect anatomical variations more frequently (Troiano and McCarthy, 2004), but a high index of suspicion in the doctor's approach is still necessary. In a recent systematic review that included studies that used more current diagnostic methods, the mean prevalence of female congenital malformations in the general population was up to ∼7% (Saravelos *et al*., 2008).

Complex malformations of the female genital tract (i.e. not only uterine or Müllerian malformations) are not very common but they do occur and are often incorrectly identified, inappropriately treated and (sometimes) incorrectly reported. The main reasons for frequent diagnostic delay and/or inappropriate surgery are as follows: (i) not considering the malformation as a cause of the patient's clinical symptoms, and (ii) not considering the embryological origin of the different constituent elements of the genito-urinary tract (Acién, 1992; Acién *et al*., 2004a). Embryological hypotheses vary (Koff, 1933; Gruenwald, 1941; Muller *et al*., 1967a; Forsberg, 1973; Ulfelder and Robboy, 1976; Marshall and Beisel, 1978; Bok and Drews, 1983; Ludwig, 1998; Sánchez-Ferrer *et al*., 2006), and the direct cause of the majority of anomalies is not known. However, the pathogenesis of the majority of these anomalies can be correctly explained and understood through the embryological hypothesis for the female genital tract presented in Acién (1992) and revised in Acién *et al*. (2004a), Sánchez-Ferrer *et al*. (2006) and Acién and Acién (2007).

As mentioned already, many women with genital tract malformations are asymptomatic, but others suffer from a wide range of symptoms and problems that may present at any age and at any time. In general, symptoms depend on the type of anomaly and the reproductive age; the following are the most frequently observed: (i) amenorrhoea in Müllerian ageneses, (ii) intra and postmenstrual dysmenorrhoea in obstructive anomalies, (iii) postmenstrual bleeding in communicating uteri, (iv) obstetric complications and repeated reproductive losses in the uterine malformations that are due to a lack of fusion or to a retention of the apposed walls of the paired ducts (lack of resorption), (v) pelvic tumours that are caused by the retention of menstrual debris and endometriosis and (vi) extra-gynaecological problems (urinary, skeletal or auditory).

Naturally, therapeutic approaches are equally variable due to the diversity of anomalies, clinical presentations and combinations. Moreover, when needed, therapy will always be surgical and will frequently be simple procedures but therapy is not necessary in the majority of malformations. However, it is absolutely necessary that the correct diagnosis is made and, therefore, an adequate classification of the malformation to avoid unnecessary or inadequate interventions is required. Certainly, the most controversial aspect of genital malformations is that their correct diagnostic evaluation and classification should be based on aetiopathogenic knowledge of the anomaly and the suspicion of other associated anomalies that may exist, so suggesting the appropriate therapeutic strategy. However, most current classifications do not seem to meet these criteria.

Objectives

The objectives of this work included the following: (i) to present the results of a systematic review of the diverse classifications of female genital tract malformations, unifying concepts and critically analysing the classifications; (ii) to comment on cases and series where a correct initial typification would have led to a better treatment, avoiding unnecessary surgery or re-surgeries; and (iii) to propose an updated classification of genitourinary malformations that integrates the current embryological and pathogenic concepts and that is clinically applicable and useful.

Embryological considerations

These considerations are available as Supplementary data SI, but briefly we must state here that: (i) The appropriate development, fusion and resorption of the separating wall between both Müllerian ducts seem to be induced by the Wolffian ducts, which are located on both sides of the Müllerian ducts and act as guide elements. (ii) The fused Müllerian ducts form the uterus up to the external cervical os, and the inducing mesonephric ducts regress cranially, though they enlarge caudally from the level of the cervical os, form the sinuvaginal bulbs, incorporate the Müllerian tubercle's cells and give rise to the vaginal plate (the cavitation of which is covered by Müllerian cells

with a cuboidal or paramesonephric epithelium). Then by metaplasic induction or by epidermization from the sinus, the vagina is covered by a flat, squamous, stratified epithelium. (iii) Because the ureteral bud sprouts from the opening in the urogenital sinus of the Wolffian duct, the absence or distal injury of one of these ducts will give rise to renal agenesis, a blind or athretic ipsilateral hemivagina and a uterine anomaly (fusion or resorption defect) due to a failure of the inducing function of the injured mesonephric or Wolffian duct. (iv) In the absence of formation and caudal growth of the urogenital wedge, there is persistent urogenital sinus and then the opening of the vagina into the sinus can be seen as a vesicovaginal fistula just underneath and between both uretheral orifices. (v) The female gubernaculum is likely formed by muscle fibres that are not of a mesonephric or paramesonephric origin and their attachment to the Müllerian ducts allows or induces the fusion and adequate development of the uterus. Thus, dysfunction of the female gubernacula probably results in female genital tract malformations.

Methods

Literature search strategy

A diligent and comprehensive search of PubMed, Scopus, Scirus and ISI webknowledge was performed for all studies published prior to 15 August 2010, using the following search terms: either 'classifications', 'classes', 'embryological' or 'embryology' in combination with either 'female genital malformations', 'female genital tract malformations', 'female genital tract anomalies' 'müllerian malformations' or 'müllerian anomalies'. The MeSH terms 'genital malformations', 'renal agenesis', 'hydrocolpos', 'blind or imperforated hemivagina' and 'uterine duplication' were also used in the search of a list of all publications containing these terms from 1950.

Next, we reviewed the following historical collections: (i) all gynaecology or obstetrics and gynaecology books that were accessible through our library and included a chapter on female genital tract malformations; and (ii) all publications about female genital tract malformations prior to 1950 that were accessible through our library. Chapters and papers were reviewed, as well as their bibliographic references that included the same terms listed already.

Selection criteria

Initially, only the studies that did not investigate malformations and/or the embryology of the female genital tract were excluded. Therefore, all of the studies, case reports and reviews that referred to anomalies or the embryology of the female genital tract and met the previous search term criteria were considered, which yielded a total of 1260 articles from the listed electronic databases and historical collections. The titles and abstracts were analysed to determine whether classification, embryology or embryological origin of genital malformations were mentioned; we also included general reviews about female genital tract malformations, case reports and case series where classification, diagnosis or management could be queried. In addition, references of all relevant articles were hand-searched for additional citations. The only exclusion criterion for 'classifications' was that there was not a classification of uterine or female genital tract malformations. There were no language restrictions.

Data extraction

Subsequently, we looked for and analysed the 124 full-text articles or book chapters that included any 'classification' of uterine malformations or of any part of the female genital tract; 20 were published before 1950. All of these articles were obtained as follows: from their journals or books, in PDF form from electronic databases, as copies forwarded by their authors and through interlibrary loan services at our University. Only five old papers (Cruveilhier, 1842; von Rokitansky, 1859; Kaufmann, 1922; Graves, 1928; De Lee, 1938) could not be obtained, but their classification system was extracted from subsequent comprehensive works (Ombredanne and Martin, 1905; Piquand, 1910; Taylor, 1943; Jarcho, 1946; Danforth, 1986).

Another 1136 articles or book chapters were excluded from the systematic review for 'classifications' for not including any classification of female genital malformations. Nevertheless, 142 of them were considered and analysed for genitourinary embryological aspects, and 194 additional papers were considered for a critical analysis of case reports or case series where classification, diagnosis or therapeutic management could be queried. As mentioned already, all relevant articles were analysed for additional citations.

Critical appraisal

The 124 publications that included 'classifications' of female genital tract malformations were studied and divided into five groups: (i) those that included a general classification (more or less original) of the malformations of the entire or part (e.g. uterus, vagina or cloacae) of the female genital tract (49 publications, 15 of which were published before 1950 and 34 after 1950); (ii) those that included a modification of previous classifications (15 publications, five of which were published before 1950); (iii) those that exposed cases with more or less complex malformations without following a determined classification (11 publications); (iv) those that conducted a critical analysis of the existing classifications without presenting a new one (4 publications); and (v) those that exposed a classification that had been already published by the same or different authors (45 publications). A Flow Diagram is included (Supplementary data, Fig. S1a).

Results

Of the 49 publications containing an original classification system, only 13 were global or general classifications, including all the genital or genitourinary tract; 24 were classifications of uterine anomalies, 3 of vaginal anomalies, 4 of utero-vaginal anomalies, 2 of segmentary atresias and obstructive anomalies, 2 of concomitant genitourinary malformations and 1 of cloacal anomalies.

Evolutionary analysis of the existing classifications

The first classifications of female genital tract malformations (and particularly of uterine malformations) from which we collected data were published in the mid-nineteenth century (Cruveilhier, 1842; Foerster, 1853; von Rokitansky, 1859); these classifications were already based on embryology and Müllerian duct development. Later, during the first half of the twentieth century, many other classifications were proposed: Ombredanne and Martin (1905), Strassmann (1907), Piquand (1910), Forgue and Massabuau (1917), Kaufmann (1922), Stoeckel and Reifferscheid (1926), De Lee (1938), Way (1945), Jarcho (1946). However, until 1950, all of the utero-vaginal malformation classifications were based on the same embryological development considerations: fusion and development anomalies of the Müllerian ducts, including rudimentary development, gynatresias and asymmetries (Masson and Kaump, 1937). After 1950, classifications were

based on different aspects: (i) formation, fusion, resorption and development of the Müllerian ducts, as in the examples shown in Netter's atlas (1979). Other classifications distinguish between vertical and lateral fusion defects of the Müllerian ducts, and others also include anomalies of the rest of the female genital tract. (ii) on the embryologic origin of the different elements of the genitourinary tract; or (iii) describe concomitant malformations of the reproductive and urinary system; or (iv) are functional classifications essentially referring to the reproductive results; or (v) based on the various altered anatomic structures or, more appropriately on the anatomic or morphologic level of the anomaly; or (vi) are partial classifications referring only to certain anatomical areas, such as vaginal anomalies, those of the cloacae, etc.

An expanded evolutionary analysis of the existing classifications is available in Supplementary data SII; and a table showing year, authors and comments on the articles included in the first four points of the critical appraisal section is also included.

Unifying terms and concepts

Buttram (1983) reported that the terminology used in the past was imprecise or inconsistently used. Data regarding abortion rates and obstetric complications in patients with unicornuate or didelphic uteri were frequently combined under the heading 'hemiuterus' and were not accessible for the evaluation of the individual anomalies. A similar difficulty arises due to the use of the term 'double uterus' to refer to both bicornuate and septate uteri. In Buttram's opinion, these terms should be abandoned. Jones (1953) also mentioned that there were two disadvantages to all previous classifications (Taylor, 1943; Way, 1945; Jarcho, 1946). First, most of the classifications employed Latin terminology, which has proved rather impractical because the average obstetrician uses English terms with only casual use of Latin terms. In addition, 'bicornuate', 'double' and 'uterus didelphys' are applied so interchangeably that it may be impossible to exactly determine what those terms mean in individual contexts. Frequently, only the most obvious anomaly is described, and there is a general tendency to up-grade the anomaly that is observed. Second, the classifications conveyed little sense of function because they described the anatomy and were concealed in an unfamiliar language. Jones (1953) also mentioned that the key to understanding congenital anomalies lies in their embryology and showed that the two Müllerian systems canalize and unite into one tract at different times and at different levels. This allows for numerous combinations, ranging from the normal single uterus-single cervix-single vagina to complete 'uterus didelphys' with doubling at all levels. Therefore, after analysing the 'single', 'septate', 'bicornuate' and 'double' concepts, Jones compiled the 25 possible combinations of the uterus–cervix–vagina triad, as shown in Fig. 1A. Jones (1953) already reported the independence of the duplication anomalies of the uterus–cervix–vagina, which is similar to what we recently presented (Acién *et al.*, 2009) to clarify the anomalies that were being published as 'Müllerian anomalies without a classification'. Those anomalies correspond to the different transitional forms of Müllerian anomalies, which range from the didelphys-unicollis uterus to the normal but bicervical uterus with or without septate vagina (Fig. 1B), based on the bidirectional theory of septum resorption published by Muller *et al.* (1967a, b). The embryologic hypothesis of Müller *et al.* (1967a) states that fusion and septum resorption begin at the isthmus and proceed simultaneously in both the cranial and the caudal directions.

Traditionally, uterus didelphys occurs when there is duplication of the vagina, cervix and uterus, and Jarcho (1946) previously reported the confusion with this term because some writers used it only for cases in which there were two separate parturient canals and bipartite vulva, which is an extremely rare condition. Jarcho (1946) cited the very unusual case reported by Gemmell and Paterson in 1913. Therefore, many authors used the term 'uterus pseudodidelphys' to denote duplication of the uterus, cervix and vagina that was not accompanied by duplication of the vulva. However, this classification does not seem correct, with the exception of one published case. In addition, Jarcho (1946) described the 'uterus duplex bicornis bicollis' vagina simplex, which chiefly differs from uterus didelphys by the absence of duplication of the vagina. Jones (1953) used the term 'bicornuate' uterus to refer to a forked fundus with a single or septate cervix; he reserved the term 'double uterus' for paired uteri, each of which has a distinct cervix of its own. He equally distinguishes between 'double or septate' cervix, which in general is easily observed, whereas distinguishing between 'septate or double' vagina is not simple. We think the duplication of the utero-cervix–vagina, with clear separation of the first two elements, corresponds to an actual didelphys uterus. However, regarding the possible discrepancy between the inferior and superior uterine segments with respect to the process of Müllerian fusion (Acién *et al.*, 2009), the term 'didelphys' might also be used in the case of complete separation of the superior segment with a normal inferior one (didelphys-unicollis uterus). A different anomaly is the bicornuate-bicollis uterus, where most of the uterine body and the inferior uterine segment are fused (see figure from Netter's atlas in Supplementary data SIII). However, in our opinion, the term 'double uterus' should not be used because it is confusing. The terms 'two hemiuteri', a 'double uterine cavity' and even 'utero-vaginal duplicity' can be used to refer to the abnormal and complete unification defects of the Müllerian ducts but not as the identification term or classification of a genital anomaly.

Another controversial point is the differentiation between a bicornuate and septate uterus. While the reproductive results are different, the traditional diagnostic tool for uterine malformations has been hysterosalpingography (HSG), and this does not enable the distinction between a bicornuate and subseptate uterus in many cases (which instead requires laparoscopic observation). For this reason, these cases have been frequently aggregated under the term 'double uteri', which refers to both the bicornuate uterus and the septate uterus (Buttram, 1983). In addition, the distinction is as important for the treatment of symptomatic patients (Strassmann metroplasty versus hysteroscopic resection). Two-dimensional transvaginal ultrasound, as well as sonohysterography (which is a three-dimensional computerized ultrasound reconstruction of the uterine cavity) and magnetic resonance imaging, has ushered in a new era of non-invasive diagnosis of uterine anomalies. All of these improvements, together with advances in the field of endoscopy (hysteroscopy and laparoscopy), have greatly increased the efficacy for an accurate, clear and detailed estimation of the anatomy of the female genital system (Grimbizis and Campo, 2010), though we think the HSG to be the basic tool in the diagnosis of genital malformations.

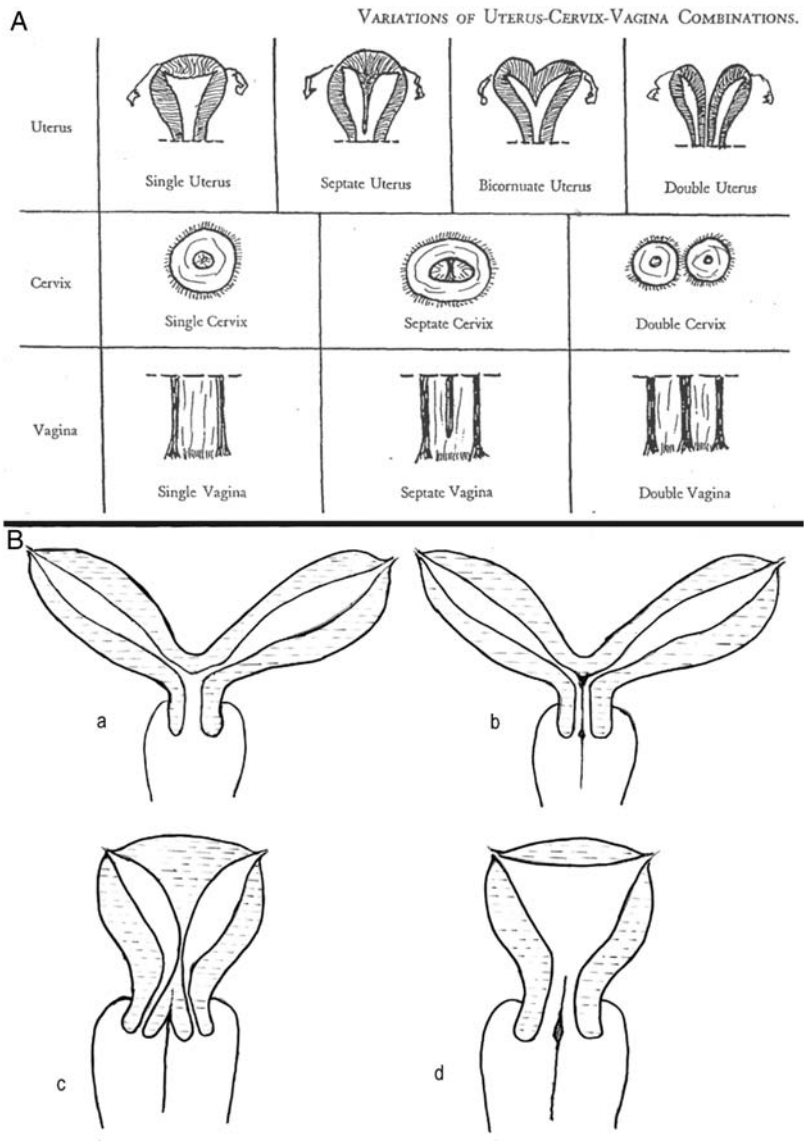


Figure 1 (**A**) Variations of uterus–cervix–vagina combinations in the female genital tract malformations according to Jones (1953). (**B**) Transitional forms of Müllerian anomalies from the didelphys-unicollis uterus to the normal but bicervical uterus, with or without septate vagina, according to Acién *et al.* (2009) (with permission).

Anyway, a collective understanding from the anatomical point of view that is independent of the methods used for the adequate identification of uterine anomalies is required; uterine anomalies should be catalogued according to the American Fertility Society (AFS) classification with a few variations, as described in Supplementary data SIII.

Critical analysis of current classifications

As seen already, all of the classifications of uterine malformations from the mid-nineteenth century to the present have been based on the Müllerian development processes. Although the variations in the lateral and vertical fusion defects from Rock and Jones (1977, and other articles from these authors) and the communicating uteri (Musset *et al.*, 1968; Toaff *et al.*, 1984) seem to complicate the classifications, they do not significantly change them. Therefore, the problem is that these exclusively Müllerian embryologic classifications are not sufficient to explain (and consequently to detect or treat) other female genitourinary malformations.

The most basic and widely used classification from Jones (1981) divided the Müllerian anomalies into three groups: agenesis, vertical fusion defects (obstructive and non-obstructive), and lateral fusion defects (obstructive and non-obstructive or symmetrical and asymmetrical anomalies). However, Buttram and Gibbons (1979), Buttram (1983) and Buttram and Reiter (1987) also introduced a classification system of the Müllerian (uterine) anomalies, which (with few modifications) was then adopted and recommended for general use by

the AFS (currently American Society for Reproductive Medicine, ASRM) (1988). Buttram (1983) mentioned that classifications used in the past were helpful but were either too simple or too complex. Therefore, Buttram and Gibbons (1979) published their classification that (in their opinion) introduced greater clarity and the potential for uniformity because it divided the anomalies into groups with similar clinical manifestations, treatment, and prognosis of pregnancy outcome. They also reported that their classification was similar to that suggested by Jarcho in 1946 and later modified by Fenton and Singh (1952).

The AFS's (1988) classification consists of seven basic groups that were essentially analysed based on Müllerian development and its relationship to fertility: (i) agenesis and hypoplasias, (ii) unicornuate uteri, (iii) didelphys uteri, (iv) bicornuate uteri, (v) septate uteri, (vi) arcuate uteri and (vii) anomalies related to diethylstilbestrol-exposure (DES) syndrome. Additional findings referring to the vagina, cervix, Fallopian tubes, ovaries and urinary system must be separately addressed.

Grimbizis and Campo (2010) reported that the basis for the AFS classification system is the anatomy of the female genital tract, especially the uterine anatomy, and that this system is simple, user-friendly and adequately clear. It has been successfully adopted as the main classification system for almost two decades because the vast majority of the female congenital malformations are uterine, which is the basic characteristic for patient grouping that explains the wide acceptability of the classification scheme. In addition, the classification of congenital malformations according to the degree of uterine deformity seems to correlate well with patient prognoses, mainly in terms of the impact on pregnancy outcome, which is another notable parameter for explaining the system's acceptance.

However, many problems are associated with the use of the AFS classification system, including: (i) it does not encompass many congenital utero-vaginal anomalies and complex genitourinary anomalies, and it is ineffective for classifying complex anomalies; (ii) class I includes cases with hypoplasia and/or dysgenesis of the vagina, cervix, uterus and/or adnexae, and the grouping of these patients into one category is very general and not functional; and (iii) obstructive anomalies, which are the result of cervical and/or vaginal aplasias and/or dysplasias, in the presence of either a normal or deformed but functional uterus are not represented. Therefore, it appears that this classification system 'could function as a framework for the description of anomalies rather than an exhaustive list of all possible anomaly types' (Grimbizis and Campo, 2010). In practice, we believe that the AFS classification, which is well known and similar to the simpler classification by Jarcho (1946), is adequate for identifying uterine malformations. Indeed, we retain the AFS classification for identifying Müllerian anomalies inside the general classification of genital malformations that we are proposing in this article.

The Jones and Rock classification (Jones, 1981; Rock *et al*., 1983; Rock and Schlaff, 1985; Rock, 1992; Jones, 1998) includes complex malformations among the vertical fusion defects but considers them as Müllerian anomalies, does not involve their origin or pathogenesis and does not cover the expectations that a generally accepted classification should. Other classifications have been based on the following: (i) functional aspects, such as the potential capacity of the uterine cavity and its musculature (Semmens, 1962) or the reproductive results (Jones and Jones, 1953); (ii) some contain only obstructive malformations of the uterus and vagina (Pinsonneault and Goldstein, 1985); or (iii) some others consider only punctual aspects, such as communicating uteri (Musset *et al*., 1968; Toaff *et al*., 1984).

More recently, Oppelt *et al*. (2005) proposed the morphological and anatomical VCUAM (Vagina, Cervix, Uterus, Adnex, and Associated Malformation) classification. In our opinion, this classification system is complex and does not suggest the origin or the pathogenic mechanism of the malformations. Further, the malformation that is represented by 'V0,C0,U4a,A#,M#' is not easily elucidated without the use of the appropriate tables. Grimbizis and Campo (2010) reported that this approach provides the opportunity for a precise, detailed and extremely representative manner of classification. Indeed, each type of anomaly can be described using this system, and the clinician will have an accurate idea of each individual's genital tract anomaly. However, as Grimbizis and Campo (2010) mention, 'the main disadvantage of this system is that it is not simple or user-friendly'. Additionally, because it is only a nomenclature for the detected anomalies, it does not make the clinician consider other undetected but associated anomalies. For example, a unicornuate uterus identified as a 'V0C0U4aA#M#' malformation could have a non-communicating cavitated horn, cervicovaginal atresia, segmentary atresia or renal agenesis on the contralateral side or even agenesis of all of the urogenital ridge derivates.

Netter's atlas includes the classification of uterine anomalies and also special cases with septate vagina and normal uterus, cases with atretic hemiuterus and cases with blind hemivagina, which—we currently know—are always associated with ipsilateral renal agenesis. In addition, in the Stoekel classification, complex malformations related to hypoplasia or rudimentary cavitated horns in Mayer–Rokitansky–Kuster–Hauser (MRKH) syndrome cases are illustrated together with classical anomalies. Alternatively, Musset *et al*. (1967a) described four groups or families of malformations of the female genital tract, and Rossier *et al*. (2008) compared in a table the 'classification of Musset (1964)' (that we have not found) and that of the AFS (1988) (mentioned above). Except for the added subtypes, there are no other differences or advantages between the systems.

Musset *et al*. (1967b) also identified three possibilities that are associated with unilateral renal agenesis (i.e. bicornuate bicervical or didelphys uterus with blind hemivagina, didelphys uterus with cervico-vaginal atresia, and bicornuate bicervical communicating uteri with blind hemivagina), thus suggesting a common embryological origin for these genitourinary malformations. However, in 1953, Woolf and Allen determined several possible associations of uterine or genital tract malformation with renal agenesis, which are always ipsilateral and are considered a consequence of mesonephric anomaly. If both kidneys are present, this anomaly does not exist. We believe that Woolf and Allen collected all possibilities of the association between genital malformations and renal agenesis in an exceptional body of work from 57 years ago (see Supplementary data SIV).

In addition, Magee *et al*. (1979) suggested an embryological classification for genitourinary malformations and identified three types of unilateral renal agenesis: (i) type I unilateral renal agenesis correlated with agenesis of all derivates from a urogenital ridge; (ii) type II, which corresponds to blind hemivagina; and (iii) type III, which (when correctly identified) corresponds to secondary renal atrophy.

In fact, we currently know that the mesonephric or Wolffian ducts are as important as the Müllerian ducts and the Müller tubercle. These

are fundamental for the adequate development of the female genital tract, especially considering the above mentioned following three key points: (i) the embryological development of the human vagina does not proceed from the urogenital sinus and Müllerian ducts (as classically thought) but from the Wolffian ducts and Müllerian tubercle; (ii) the appropriate development, fusion and resorption of the separating wall between both Müllerian ducts is induced by the Wolffian ducts that are located on both sides and act as guide elements; and (iii) the Wolffian ducts, in their opening in the urogenital sinus, sprout and exit through the ureteral bud to form the kidneys in the metanephros. Therefore, a mesonephric lesion will promote a vaginal anomaly, a uterine anomaly and ipsilateral renal agenesis (Acién and Acién, 2010a).

The embryological and clinical classification that we proposed in 1992 (Acién, 1992) and modified in 2004 (Acién *et al*., 2004a) is based on these concepts. As shown in Acién *et al*. (2004a), there were four locations for the origin of five groups of malformations: (i) agenesis of an entire urogenital ridge, (ii) mesonephric anomalies, (iii) Müllerian anomalies, (iv) cloacal anomalies and (v) malformative combinations. This clinical-embryologic classification may seem complex but any genital malformation classification that allows their correct cataloguing and the proper planning of therapeutic strategies should include the embryological aspects described earlier. This classification system could lead to a better understanding of the pathogenesis of female genital tract anomalies, and we believe that it includes essentially all genitourinary anomalies and helps as a diagnostic tool, as well as facilitates the thorough preparation of the surgical correction of these anomalies. However, our classification system has also been criticized. Grimbizis and Campo (2010) reported that there is a radical change in the fundamentals of our classification system from anatomy (which is the basis for the widely accepted AFS classification system) to embryogenesis, and this reduces its chances of acceptance. Moreover, our classification system is claimed not to be very simple or user-friendly. However, the AFS's classification is only for uterine anomalies. We think that our system is the most appropriate classification scheme to understand and diagnose a malformation and its associated anomalies, as well as to achieve more appropriate correction when necessary. The update of our own classification system that we are proposing in this paper tries to prove it.

Comments and proposition for an updated classification

Frequently, we see patients with genital malformation in which the therapeutical procedure followed shows that the pre-surgery diagnosis, and usually the post-surgery one, has not been the most correct. The same is found with many cases reported in the literature. In Supplementary data SV, we present some examples. This commonly happens because the physician did not bear in mind the embryology of the female genitourinary tract when establishing an aetiopathogenic diagnosis and, consequently, designing a therapeutical strategy. Naturally, we do not mean the usual uterine malformations, but those complex associated genito-urinary anomalies, certain anomalies of the urogenital sinus and malformative combinations. In the case of an anomaly that could be easily solved, the treatment applied might be occasionally so complex that it leads to unnecessary complications. That is the reason why we insist on the embryology and pathogenesis of genital malformations and on proposing a classification system which, based on this knowledge, suggests the appropriate therapeutical strategy.

We agree with Grimbizis and Campo (2010) when referring to the need for a new classification system that is as clear, easy and exact as possible; they report that clarity will enable clinicians to develop diagnostic strategies and that anatomy of the female genital tract should be defined as objectively as possible. However, only exactly describing the findings, as in the Oppelt *et al*. (2005) classification, is not adequate. The classification system should suggest other associated anomalies, and though the 'clear definitions of each type may help to avoid subjectivity in the criteria used to recognize and classify each anomaly' (Grimbizis and Campo, 2010), it will not avoid the 'transitional cases', which normally occur. Often between one anomaly and another, there are transitional cases that the clinician will have to decide whether to allocate to one group or another based on the analysis of the complementary explorations and the appropriate knowledge of the embryology and pathogenesis. Classifying other transitional cases also depends on the acceptance of the bidirectional septum resorption theory (Muller *et al*., 1967a, b) described already. Therefore, even though Grimbizis and Campo (2010) state that many publications have reported a number of new variations of undescribed anomalies with unclear classification (e.g. septate bicervical uterus), those variations were already addressed by Jones (1953). Moreover, there are the complex genito-urinary malformations and the malformative combinations mentioned already.

On the basis of the Müllerian development processes, we could naturally consider as a good classification of the female genital malformations the following:

(i) Anomalies due to total or partial agenesis of one (unicornuate uterus) or both Müllerian ducts (MRKH syndrome);
(ii) Anomalies due to total or partial absence of fusion, i.e. didelphys uterus and bicornuate (bicollis and unicollis) uterus;
(iii) Anomalies due to total or partial absence of the reabsorption of the septum between both Müllerian ducts (septate and subseptate uterus);
(iv) Anomalies due to a lack of later development (hypoplastic uterus, T-shaped and DES syndrome); and
(v) Segmentary defects and combinations of different anomalies.

However, this classification scheme, similar to Jarcho's classification (1946) and to that of the AFS (1988), only refers to Müllerian anomalies and does not address the rest of the elements or the origin of the female genitourinary tract.

Therefore, after considering the embryological concepts described in the introduction and in Supplementary data SI and the correlation between the adult derivatives and female abnormalities of embryonic urogenital structures; analysing the results of the systematic review; reviewing the unification of terms and concepts on genital malformations (see also Supplementary data SII); and after critically considering the current classifications, we have the basis: (i) to comment on series and case reports that can now be better understood as much in diagnosis as in the adopted therapeutical management, sometimes with inadequate operation (see Supplementary data SV); and (ii) to propose a classification system of the female genital tract malformations that necessarily will be a modification and update of our

clinical-embryological classification, and that has the fundamental interest of correlation with the clinical presentation, of inducing the search for other associated anomalies and, in particular, of suggesting the most simple and appropriate therapeutical procedure.

Proposed updated embryological-clinical classification for female genitourinary malformations

In Table I we propose a simplified scheme that includes six groups of female genitourinary anomalies, and besides a practical and illustrated application of the proposed classification correlating the ethiopathogenia, the anatomical findings, the diagnosis and the clinical symptoms are included to aid clinicians in Table II. The therapeutic strategy must be based on the logical deduction product of the aetiopathogenic knowledge of the anomaly and on the experience of clinicians (Acién and Acién, 2004c).

The expanded and updated embryological-clinical classification includes:

(i) *Agenesis or hypoplasia of an entire urogenital ridge*. In these cases, there will be an absence of a kidney, functioning ovary, Fallopian tube, hemiuterus and hemivagina (undetectable) on the same side. Obviously, we will find a unicornuate uterus on the side contralateral to the agenesis. Cases may be also associated with vertebral and/or auditory anomalies (Acién *et al.*, 1991, 2010c) and can present in two different forms:

  (a) With bilateral Müllerian agenesis: Rokitansky syndrome with unilateral renal agenesis; and
  (b) Unicornuate uterus with contralateral renal agenesis.

(ii) *Mesonephric anomalies with an absence of the Wolffian duct opening into 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 'inducting' function of the injured mesonephric duct on the Müllerian duct (uterine duplicity with/without interseptal or interuterine communication) (Acién and Acién, 2010a). If there is an ectopic sprout of the ureteral bud, there could then be renal hypoplasia and ectopic ureter opening into the blind vagina (Acién *et al.*, 1990, 2004b). These are the most complex malformations, they may appear as uterine duplicity (didelphys, bicornuate and, rarely, septate uterus) and present with the following:

  (a) Large hematocolpos in a blind hemivagina, with ipsilateral renal agenesis;
  (b) Gartner's pseudocyst in the anterolateral wall of the permeable vagina (frequently as a Herlyn-Werner syndrome) with ipsilateral renal agenesis;
  (c) Partial reabsorption of the intervaginal septum (sometimes as a vaginal septum observed only in the superior half of the vagina or seen as a buttonhole on the anterolateral wall of the permeable vagina); and
  (d) Complete unilateral vaginal or cervico-vaginal agenesis with or without communication between both hemiuteri. In the first case, with communication, the HSG image has the aspect of a bicornis-unicollis uterus. The second case (without communication) usually presents with haematometra, retrograde menstruation and endometriosis from a cavitated rudimentary horn, and worsening of symptoms if the tube or adnexa are removed. Ipsilateral renal agenesis will also be present.

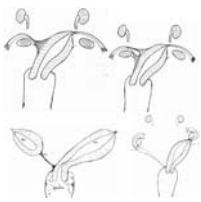
(iii) *Isolated Müllerian anomalies*. This group includes the common isolated uterine anomalies that can be classified according to the AFS (or ASRM) system, with the modifications described earlier. These Müllerian anomalies can affect the following:

  (a) Paramesonephric or Müllerian ducts: tubarian (duplicity, segmentary atresia) and uterine malformations showing agenesis, lack of fusion, absence of reabsorption or lack of later development, as in the AFS classification:
    (1) Agenesis and uterine hypoplasias;
    (2) Unicornuate uterus, which is generally accompanied by athretic rudimentary horn and normal adnex on the other side, but a rudimentary cavitated and non-communicated horn can also be present;
    (3) Didelphys uterus;
    (4) Bicornuate uterus: complete (bicornis-bicollis uterus) and partial (bicornis-unicollis uterus).
    As described already, some cases of bicornis-unicollis uterus can have a cavitated non-communicating horn, and its inclusion in a bicornuate or unicornuate uterus is discussed. Functionally, it is a unicornuate uterus but it is important to adequately identify the anomaly, to determine if there is renal agenesis and to decide if surgical correction is required;
    (5) Septate uterus: complete and partial or subseptate uterus;
    (6) Arcuate uterus; and
    (7) Anomalies related to DES syndrome, also including hypoplastic and T-shaped uterus.

Table I Embryological-clinical classification for female genito-urinary malformations (revised and updated from Acién, 1992; and Acién *et al.*, 2004a).

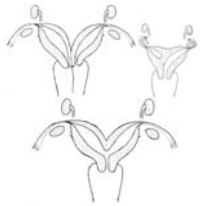
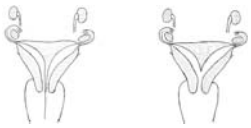
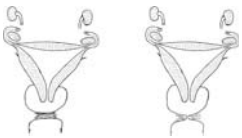
1. Unilateral genito-urinary agenesis or hypoplasia
They are the cases of unicornuate uterus with contralateral renal agenesis due to agenesis or hypoplasia of an entire urogenital ridge
2. Uterine duplicity (bicornuate or didelphys uterus) with a blind hemivagina (or unilateral cervico-vaginal atresia) and ipsilateral renal agenesis
It includes the Herlyn–Werner and Wunderlich syndromes and there can also be cases of resorption partial of the intervaginal septum
3. Isolated or common uterine or utero-vaginal anomalies
They include the anomalies in the Müllerian development processes also included in the classification of the American Fertility Society without other associated anomalies; and also the transverse vaginal septum
4. Accessory uterine masses with an otherwise normal uterus, and other possible gubernaculum dysfunctions
5. Anomalies of the urogenital sinus
As imperforated hymen, vesico-vaginal fistulas, persistent urogenital sinus, cloacal anomalies, and other external gastrointestinal or urinary anomalies
6. Malformative combinations

Table II Illustrated relationship and classification of the pathogenic findings and anatomical figures with symptoms and pathology name, following an updated embryological and clinical classification of female genital tract malformations.

Aetiopathogenic anomaly	Anatomical findings	Pathology name	Clinical symptoms
1. Unilateral genito-urinary agenesis or hypoplasia			
1.1 With contralateral müllerian agenesis		Rokitansky syndrome with URA	Primary amenorrhoea
1.2 Without contralateral agenesis		Unicornuate uterus with contralateral RA	No symptoms. Reproductive Breech present
2. Uterine duplicity with a blind hemivagina (or atresia) and ipsilateral RA, showing			
2.1 Large hematocolpos, blind hemivagina		Didelphys or bicornuate uterus with blind hemivagina and ipsilateral RA	Pain. Intra and postmenstrual dysmenorrhea Pelvic tumour Postmenstrual spotting
2.2 Like Gartner's pseudocyst		Bicornuate communicating uterus, athretic blind hemivagina and ipsilateral RA. Herlyn-Werner syndrome	Pain? Cyst in anterolateral wall of vagina. Postmenstrual spotting or vaginal discharge.
2.3 Partial reabsorption of the vaginal septum		Didelphys or bicornis-bicollis uterus with a short septum or buttonhole, and URA	No symptoms. Dyspareunia. Reproductive. Breech presentation. Obstetrical complications
2.4 Complete unilateral vaginal or cervico-vaginal atresia with communicating uteri		Bicornis-unicollis uterus with an anomalous horn and ipsilateral RA	No symptoms Reproductive Breech presentation Obstetrical complications
2.5 Idem, without communicating uteri		Unicornuate uterus with contralateral unattached but cavitated rudimentary horn URA	Pain. Increasing dysmenorrhea after surgery? Symptoms as endometriosis
3. Isolated or common uterine or utero-vaginal anomalies, affecting			
A. Paramesonephric or müllerian ducts			
A.1. Agenesis or hypoplasias		Müllerian agenesis	Primary amenorrhoea Endometriosis and criptomenorrhea if cavitated horn
A.2. Unicornuate uterus with atretic cavitated or non-cavitated rudimentary horn, or segmentary atresia, or 'unilateral Rokitansky syndrome'		Unicornuate uterus; or bicornuate with cavitated noncommunicated uterine horn or segmentary atresia	Reproductive. Breech presentation Intra or postmenstrual dysmenorrheal. Endometriosis?

Continued

Table II *Continued*

Aetiopathogenic anomaly	Anatomical findings	Pathology name	Clinical symptoms
A.3. Didelphys uterus		Didelphys uterus	Reproductive Breech presentation
A.4. Bicornuate uterus. Eventually, with a non-communicating cavitated uterine horn		Bicornis-bicollis uterus and Bicornis-unicollis uterus (non-communicating cavitated horn)	Reproductive Miscarriage. Breech presentation Inmature delivery. Retrograde menstruation
A.5. Septate uterus		Septate and subseptate uterus	Reproductive Miscarriage Breech presentation Inmature and premature delivery
A.6. Arcuate uterus		Arcuate uterus	Reproductive losses?
A.7. Anomalies related to DES syndrome		DES syndrome. Hypoplastic and T-shaped uterus. Tricavitated uterus	Infertility Reproductive losses
B. Müllerian tubercle			
B.1. Complete vaginal or cervico-vaginal agenesis or atresia		Vaginal or cervico-vaginal atresia	Primary amenorrhoea Pain Cryptomenorrhea. Endometriosis
B.2. Segmentary atresias		Complete or incomplete transverse vaginal septum	Dyspareunia? Obstetrical problems? Or primary amenorrhoea and cryptomennorrhea
C. Both Müllerian tubercle and ducts			
Complete utero-vaginal agenesis		Rokitansky or MRKH syndrome	Primary amenorrhoea
4. Accesory uterine masses and other gubernaculum dysfunctions		Accesory and cavitated uterine masses with normal uterus. Didelphic uterus without RA?	Pain Dysmenorrhea Tumor
5. Anomalies of the urogenital sinus		Imperforated hymen. Persistent urogenital sinus. Congenital vesico-vaginal fistula.	Cryptomenorrhea Pain Menuria, Hypospadias, Cloacal fistulas

Continued

Table II *Continued*

Aetiopathogenic anomaly	Anatomical findings	Pathology name	Clinical symptoms
6. Malformative combinations		Variable	Variable

URA, unilateral renal agenesis; RA, renal agenesis; MRKH, Mayer–Rokitansky–Kuster–Hauser; DES, diethylstilbestrol.

(b) Müllerian tubercle:
  (1) Complete vaginal (or cervico-vaginal) agenesis or atresia; and
  (2) Segmentary atresias as transverse vaginal septum.
(c) Both Müllerian tubercle and ducts: Rokitansky or MRKH syndrome.
(d) These Müllerian anomalies may display a discrepancy in the fusion and reabsorption processes between the superior and inferior uterine segments and segmentary defects. Some cases are also transitional.

(iv) *Gubernaculum dysfunction*. These cases are typified by accessory and cavitated uterine masses and likely by other uterus-like masses with a completely normal uterus (Acién *et al*., 2010d). Other anomalies are probable due to the lack of fusion of the Müllerian ducts, such as cavitated horns that are unattached in uterus didelphys, without unilateral renal agenesia.

(v) *Anomalies of the urogenital sinus*. This category includes cases of imperforated hymen with persistent urogenital membrane, congenital vesicovaginal fistulas (pseudo-fistula with menuria), cloacal anomalies and others that show rectovaginal fistulas and gastrointestinal or urinary tract anomalies.

(vi) *Malformative combinations*. These cases involve Wolffian, Müllerian and/or associated cloacae anomalies, sometimes with an anomaly of the ventral urogenital sinus (Acién *et al*., 2010b). Others are cases with mesonephric anomaly on one side and Müllerian anomaly on the contralateral side, eventually associated with an anomaly of the urogenital sinus (Acién *et al*., 2004); others have presented hereditary renal adysplasia, pulmonar hypoplasia and Rokitansky syndrome (Acién *et al*., 2010c).

As mentioned earlier, in groups 1 and 2 and in the combinations when affecting the mesonephric ducts, there will be renal agenesis (Acién and Acién, 2010a). In all other genital malformation types, there can also be associated urinary anomalies (e.g. ptosis and horseshoe kidney) but these may also be found in women without genital malformations.

Conclusions

(1) Current embryological knowledge shows that the mesonephric or Wolffian ducts and (likely) the female gubernaculum play a role as inductors for the adequate development and formation of the Müllerian ducts. Also, the mesonephric ducts together with the Müllerian tubercle form the vagina. The ureteral bud sprouting from the opening of the mesonephric ducts into the urogenital sinus determine the adequate formation of the urinary system and the kidneys. Any lesion of these elements will produce different female genital tract malformations depending on the location or level of the lesion. The adult derivatives and abnormalities that correlate with the different urogenital embryonary structures are also mentioned in Supplementary data SI.

(2) The majority of female genital tract malformations classifications available from the mid-nineteenth century only considered uterine (Müllerian) malformations, and they were essentially based on the lateral fusion defects of the Müllerian ducts. The AFS classification (1988) proposed by Buttram (1983) and modified from Jarcho (1946) is the most widely used. Other classifications include vertical fusion defects or obstructive anomalies, communicating uteri, the anatomic typification of the defects (VCUAM classification) or functional aspects (reproductive results). Others still are based on genitourinary embryology and classify the malformations by agenesis of an entire urogenital ridge, mesonephric anomalies, Müllerian anomalies (without associated mesonephric anomaly), cloacal anomalies and combinations thereof. The concepts and terms used to describe female genital tract malformations were analysed and must be unified.

(3) Addressing the need for an updated classification system of genital malformations that considers the experience gained from the application of the current classification systems and that is based on current embryological and aetiopathogenic knowledge, in this review an updated embryological-clinical classification of genitourinary malformations that includes correlation with anatomical findings and clinical presentation (aimed at suggesting the best therapeutic strategy) was presented.

Supplementary data

Supplementary data are available at http://humupd.oxfordjournals.org/.

Authors' roles

P.A. designed the study, made the systematic review, tables and figures, and wrote the manuscript. M.A. participated in the systematic review, helped with the bibliographic search and reviewed the manuscript. P.A. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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