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Congenital Uterine Malformations

Malformaciones Congénitas Uterinas

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SUMMARY: Congenital Uterine Malformations (CUD) are generally asymptomatic, benign and incidentally diagnosed. In order to describe the different types of CUD, it is necessary to understand its embryonic development, emphasizing at the same time the importance of the paramesonephric ducts, structures that later in development will give rise to the uterine tubes and the utero-vaginal duct. The objectives of the present study were to analyze basic aspects of the normal and pathological development of the female genital tract during embryonic/fetal development, correlating them with the histological evaluation, and relating such aspects to possible future uterine pathologies that girls could experience from the beginning. of puberty. A human fetus of approximately 8 weeks gestational age was studied. Four mouse fetuses 15 days post-coitus were also used as an animal model, of which 2 corresponded to female individuals and 2 to male individuals. The biological samples were fixed in 10% Formalin and subsequently processed using routine histological techniques and staining with Hematoxylin-Eosin. Most paramesonephric malformations mainly affect the uterus, and are characterized by the manifestation of deficits, either in the development, fusion or canalization of the paramesonephric ducts. Various developmental mechanisms, such as cell proliferation, apoptosis and epithelial-mesenchymal transformations, are essential for the normal development of the uterine tubes and the uterus. Paramesonephric malformations are generally manifested during adolescence and are usually accompanied by symptoms including pelvic pain and primary amenorrhea.

KEY WORDS: Paramesonephric ducts; Congenital uterine malformations; Müllerian anomalies.

INTRODUCTION

Disorders of the paramesonephric or Müllerian ducts (CUD) constitute a wide group of malformations affecting both the development and the morphology of the uterine tubes, uterus and upper third of the vagina. Such malformations may occur with or without associated ovarian, urinary tract, skeletal or other organs anomalies (Acién & Acién, 2011). The normal development of the female genital tract involves a series of complex processes, among which the differentiation, migration, fusion and subsequent canalization of the paramesonephric system play a fundamental role (Acién *et al*., 2011).

The paramesonephric duct is constituted by two mesodermal derivatives that in both sexes develop in a medial and caudal position, but in general, only in embryos presenting XX chromosomes they further develop, originating the female genital organs. It has been well documented that the development of the paramesonephric duct is controlled by the presence or absence of the anti-Müllerian hormone (Rey, 2001).

Anomalies of the paramesonephric duct are characterized by failures either in the development, fusion or canalization of the paramesonephric ducts. Their manifestation ranges from agenesis of the uterus and/or tubas or vagina, to slight defects such as indentation of the uterine fundus (Acién). They are, therefore, not acquired anomalies, but rather defects whose origin is found in the abnormal development of the paramesonephric ducts during intrauterine life (Acién *et al*., 2011).

Uterine disorders (CUD) are usually asymptomatic, benign and incidentally diagnosed. In general, patients usually consult due to primary amenorrhea, fertility problems or obstetric complications (Medina *et al*., 2015). Although most patients suffering CUD have normal reproductive function, some of them may present loss of function and chronic pain (Jayaprakasan & Ojha, 2022).

Various studies have described population prevalence rates that vary between 0.06 % and 38 % (Chan *et al*., 2011).

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This wide variation could be related to the evaluation of different populations under study, concomitantly with the use of different diagnostic techniques (Jayaprakasan & Ojha, 2022). The reported prevalence in the general population can reach 1 to 5 % and can reach up to 8 % of cases in women who consult in assisted reproduction centers. It has been estimated that only a quarter of women carrying these anomalies could experience reproductive difficulties (Medina *et al*., 2015).

The objectives of the present study were to analyze basic aspects of the normal and pathological sexual differentiation of the female genital tract during embryonic/fetal development, correlated with histological assessment, and to relate those aspects with possible future uterine pathologies that girls could experience, from the beginning of puberty onwards,

MATERIAL AND METHOD

In order to perform the histological analyses required to fulfill the purposes of this research, the undifferentiated gonadal area as well as the mesonephric and paramesonephric ducts of a human fetus of approximately eight weeks of gestation were used. This histological sample was obtained from the embryological anatomical collection of the Institute of Biomedical Sciences (ICBM), Faculty of Medicine, University of Chile. In parallel, and as an animal model, 4 mouse fetuses 15 days post coitus were also included. These samples were fixed in 10% formalin and subsequently processed by routine histological technique and staining with Hematoxylin-Eosin.

The present study was authorized by the Ethics Committee of the ICBM (Protocol 2024) and by the Ethics Committee for Scientific Research with Animals, of the Faculty of Medicine of the University of Chile, granted to our line of research in 2016.

RESULTS AND DISCUSSION

The paramesonephric ducts are formed during the sixth week of development as an invagination of the coelomic epithelium (Fig. 1), subsequently growing vertically in a caudal and medial direction, thus originating the uterine tubes, which turn into horizontal position, fusing their poles along the midline (Fig. 2), and giving rise to the uterine body. (9-12 week post fecundation) The caudal end of the ducts projects towards the posterior wall of the urogenital sinus, where the paramesonephric tubercle (Müller's tubercule) will form (Arteaga & García, 2014). From the 9th gestational week, through an apoptotic phenomenon regulated by the Bcl 2 gene, a regression of the uterine septum occurs, giving rise to the formation of the uterine cavity (Troiano & McCarthy, 2014).

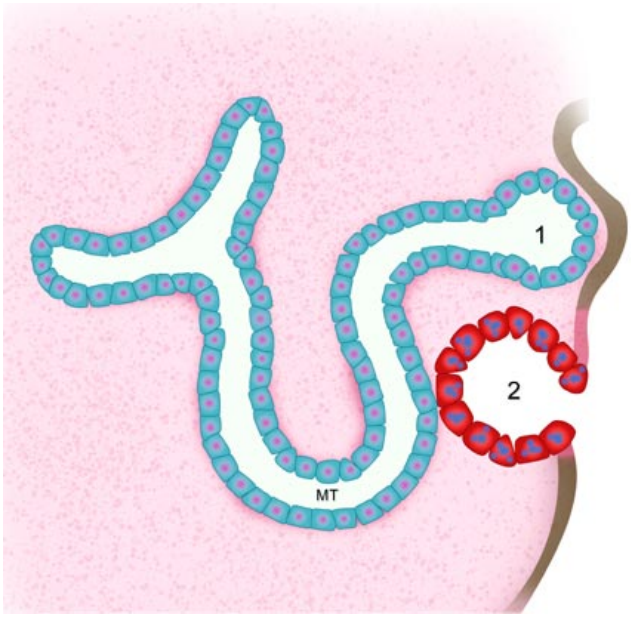

Fig. 1. Schematic representation of a cross section of the abdominal región. The developmental stage illustrated corresponds to a six-week human embryo. It depicts the mesonephric tubule (MT), as well as the mesonephric duct (1) and paramesonephric duct (2) at the time of its formation from the coelomic epithelium

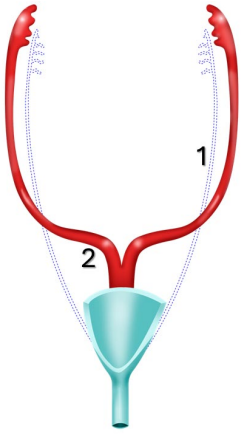

Fig. 2. Schematic representation of the paramesonephric ducts. At six weeks of gestation, the unfused segments (1) are part of the uterine tubas. At the point were both segments fuse (2) along the embryo midline, the body of the cervix is originated.

Immediately after the paramesonephric duct reaches the urogenital sinus, two solid outpouchings, called sino-vaginal bulbs, are generated from the pelvic part of the sinus. The cells that constitute the tissue of these sino-vaginal bulbs proliferate to form the vaginal lamina. These events establish an increase in the distance between the uterus and the urogenital sinus, thus giving rise to the lower two thirds of the vagina. The inside of the vagina remains separated from the outermost portion of the urogenital sinus by the hymen, which during perinatal life will form a small hole (Troiano & McCarthy, 2014). The definitive canalization from the vagina to the uterus occurs through a vacuolization process of the caudal paramesonephric tissues and the senovaginal bulbs (Fig. 3).

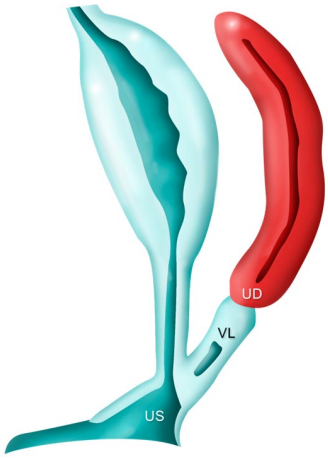

Fig. 3. Sagital schematic view of the developing reproductive structures of a female human fetus. At ten weeks of gestation, the urogenital sinus (US), uterovaginal duct (UD), vaginal lamina (VL) are fully developed.

Paramesonephric ducts can be recognized in histological sections of the embryo from the initial moment of its formation, by their cylindrical lining epithelium which displays a pseudostratification appearance, very different from the mesonephric duct, whose epithelial cells are cubic and low in height. These histological features are depicted in Fig. 4. As development progresses, the ductal system undergoes a stage of intense cell proliferation. If testicular differentiation occurs towards the male direction, the paramesonephric ducts involute through two biological developmental mechanisms that correspond to epithelia mesenchymal transformation and/or cellular apoptosis (Fig. 5). Alternatively, if the differentiation occurs in the female direction, it is the mesonephric duct that involutes through cellular apoptosis and epitheliomesenchymal transformations (Fig. 6), concomitantly; the paramesonephric duct grows and develops. The paramesonephric duct (PD) is constituted by cylindrical cells that on development and growth adopt the appearance of a pseudostratified epithelium. (Fig. 7) If the mesonephric duct (Fig. 7) does not completely disappear, cysts, also called "Gartner cysts", may appear on later development (Roa & del Sol, 2015).

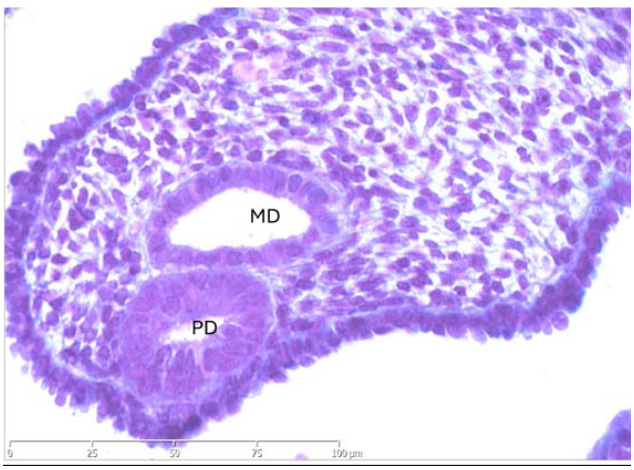

Fig. 4. Histological section of the gonoducts in a human embryo. At the beginning of the 8th week of development, the mesonephric ducts (MD) display a regular lumen lined by cubic epithelial cells. On the other hand, the paramesonephric ducts (PD) are characterized by a smaller lumen lined by a pseudostratified epithelium . H & E staining; Calibration bar: 60 *u*m.

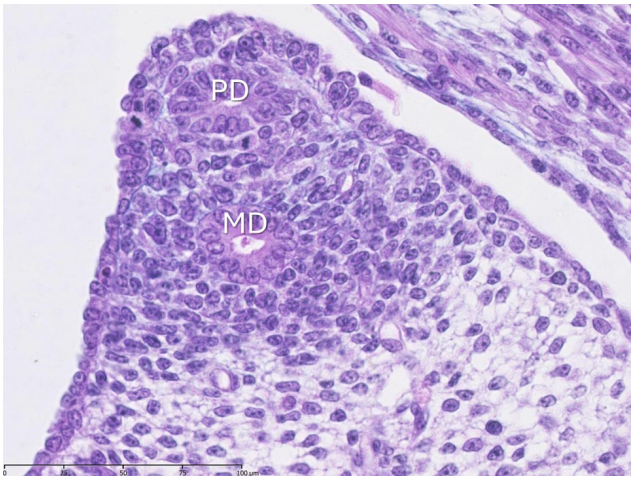

Fig. 5. Histological section of the genital tract from a mouse embryo. The involution of the paramesonephric duct (PD) is evidenced by the destruction of the epithelial cells which display pyknotic nuclei. The presence of apoptotic bodies and epithelial-mesenchymal transformations are also evidenced. H & E staining; Calibration bar: 100 µm.

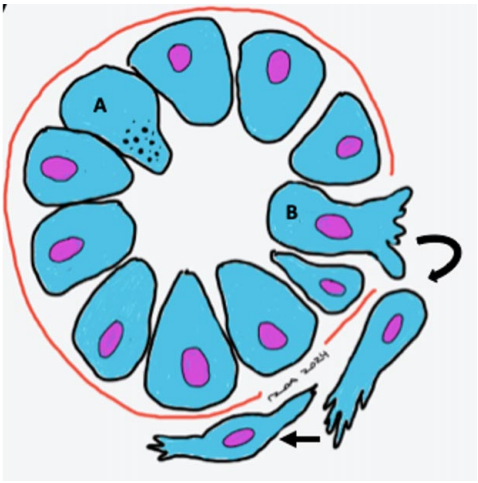

Fig. 6. Schematic illustration of the involution of the genital tract. Two different mechanisms have been proposed. The first one occurs by transformation of the epithelium into meseschymal cells (A) and the second is by cellular apoptosis (B). In addition, the basal membrane (depicted as a brown line) becomes disintegrated. "Modified from: Montenegro, M. A. & Rojas, M. A. Transformación epitelio-mesenquimática durante el desarrollo embrionario. *Rev. Chil. Anat., 19(3)*:301-10, 2001.

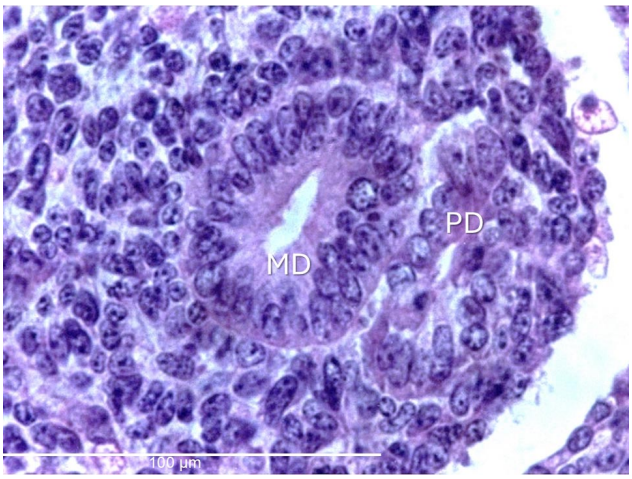

Fig. 7. Histological section of the genital tract of a 15-day-old mouse. The paramesonephric duct (PD) is constituted by cylindrical cells that on development and growth adopt the appearance of a pseudostratified epithelium. The involution of the mesonephric duct (MD) is clearly observed. H & E staining; Calibration bar: Calibration bar: 100 µm.

As it is well known, both the urinary apparatus as well as the genital system are derived from the intermediate mesoderm. Therefore, any abnormal differentiation of the mesonephric or paramesonephric ducts may be associated with nephrourologic abnormalities (Sadler, 2023). Although unilateral renal agenesis is the most common of these anomalies, others such as crossed renal ectopia, cystic renal dysplasia, horseshoe kidney and duplication of the collecting system have also been reported (Díaz *et al*., 2008).

It has been described that the initial formation of the paramesonephric ducts depends on molecular signals provided by a series of genes, among which Lim1, EMX2 and WNT-4 are the most widely studied (Jacquinet *et al*., 2016). Although most embryos with altered Lim1 expression die during gestation, some of them survive for a short time, which allows researchers to confirm the absence of derivatives of the paramesonephric and mesonephric ducts (Carlson, 2009). Mutant embryos lacking the Emx2 gene do not develop kidneys, ureters, gonads, or the paramesonephric ducts (Miyamamoto *et al*., 1997).

Regarding WNT genes, they encode glycoproteins that regulate cell growth and differentiation along the embryogenesis processes. During the first step of paramesonephric duct development, WNT-4 signaling is required for invagination of the coelomic epithelium. This is how the inactivation of WNT4 in a female embryo leads to the absence of the paramesonephric ducts WNT-5 deficiency causes short, curved uteruses, as well as poorly defined cervix and vagina (Vaino *et al*., 1999). In a similar line of evidence, it is known that WNT-7A participates in maintaining the expression of an ordered sequence of HOX genes. Deficiency in its expression causes the lack of development of uterine tubes and a uterus that looks like a vagina (Carlson, 2009).

The body of aforementioned evidence points to the fact that the differentiation of the utero-vaginal duct into a functional reproductive tract depends on the interaction between the HOX and WNT genes, which are regulated and "deregulated" by steroid hormones or their counterparts (xenoestrogens) during embryogenesis and adult life (Mericskay *et al*., 2004).

Hox genes

As previously mentioned, the molecular mechanism through which positional identity is assigned in a particular organ is related to the HOX genes. These are expressed following a temporal-spatial pattern during organogenesis (Mortlock & Innis, 1997). Particularly, the expression of HOXA9 is detected in the future uterine tuba, while the expression of HOXA-10 is evidenced in the tuba-uterus junction. In turn, HOXA-11 is strongly expressed in the uterus and less intensely in the cervix, while HOXA-13 is expressed only in the cervix and upper vagina (Carlson, 2009). Therefore, it is reasonable to assume that this so called "HOX Code" contributes in an important way to the development of the female genital tract. (Rojas & Prieto, 2014)

The normal patterns of development of the paramesonephric duct can be altered by exposure to some endocrine disrupting agents such as the synthetic estrogen diethylstilbestrol (DES). It has been shown in rats that DES exposure in utero leads to alterations in the normal pattern of expression, namely: HOXA9 is expressed in the uterus and not in the tuba, HOXA10 expressed itself in the uterus, and HOXA11 expression is greatly decreased in the womb. Furthermore, all of these genes are overexpressed in the vagina.

Another endocrine-disrupting agent similar to estrogen (xenoestrogen) is Bisphenol A (BPA), a common component of polycarbonate plastics used in food storage and dental sealants. BPA has been shown to induce dysregulation of HOXA10 (Daftary & Taylor, 2006).

Associated syndromes

It is well known that CUDs are frequently associated with anomalies of the vagina and/or kidneys. Some of these associations have been coined under specific terms or syndromatic conditions. In this regard, the Mayer-

Rokitansky-Kuster-Hauser syndrome has been described, with an incidence of 1 in 4,500-5,000 newborn females. The said syndrome is characterized by congenital absence of the uterus, cervix and the upper portion of the vagina, in a phenotypically normal woman (Jacquinet *et al*., 2016).

Another associated disorder is the OHVIRA syndrome, whose acronym corresponds to the English "obstructive hemivagina with ipsilateral renal agenesis": vagina obstructed by the vaginal septum, in the context of a bidelphytic uterus and a monorenal patient. Renal involvement occurs due to the close morphogenetic relationship in the development of the paramesonephric and mesonephric ducts, in the 9th week of gestation. An incidence of 1 in 2000 or 1 in 28,000 cases has been estimated. This syndrome requires surgical management (Paz-Montañes *et al*., 2020).

It has also been reported that the relationship of UD with kidney anomalies occurs with a high frequency, presenting an incidence of up to 40% of kidney anomalies associated with paramesonephric agenesis (Chen *et al*., 2021; Kapczuk *et al*., 2016). It should be noted that in these cases, medical assessment using imagenology is considered to be imperative.

Clinical presentation. Classification

CUDs have been described in many classification systems that have been developed for Paramesonephric Anomalies. The 1988 American Fertility Society (AFS) Classification is the most recognized and widely used. It classifies UAs into seven types: i) Uterine hypoplasia/ agenesis, ii) Unicornuate uterus, iii) Didelphys uterus, iv) Bicornuate uterus, v) Septate uterus, vi) Arcuate uterus and vii) Diethylbestro-related anomalies. Among the advantages of such classification are its simplicity, recognition, and correlation with pregnancy outcomes. Even though, the AFS classification has been criticized for its focus oriented primarily to anomalies of the uterine corpus, excluding those related to the vagina and cervix, and also for its lack of clear diagnostic criteria, as well as its inability to classify complex alterations (AFS, 1988).

The European Society of Human Reproduction and Embryology (ESHRE), together with the European Society of Gynecological Endoscopy (ESGE), developed a classification system based on the anatomy of the female genital tract, also considering its embryological origin (Jayaprakasan & Ajha, 2022). Although the ESHRE/ESGE Classification meets the needs and expectations of a large group of experts in the field, it is still not considered perfect, because it overestimates the prevalence of septate uterus (Jayaprakasan *et al*., 2022). Finally, the American Society of Reproductive Medicine Working Group for the Classification of Müllerian Anomalies recently designed a new classification system, published in 2021 (Pfeifer *et al*., 2021). This new classification was based on the 1988 AFS Classification and was expanded in order to include all categories of anomalies. However, this classification did not consider aspects of genitourinary embryology, and it was focused only on the morphological anomalies of the paramesonephric ducts, without taking into consideration that the entire urogenital crest, the urogenital sinus and the gubernaculum may also be affected (Acién & Acién 2007).

CUD are generally asymptomatic, manifesting at an early age and may occur concomitantly with an abdomino-pelvic or perineal tumor, during the period of menarche secondary to outflow obstruction (hematocolpos). These affectations may also be associated with dysmenorrhea, abnormal vaginal bleeding, primary amenorrhea, and difficulty in using tampons. Later in life, non-obstructive disorders may appear which can be diagnosed incidentally, after menarche, during the infertility study or personal history of repeated abortions; they are also usually diagnosed in patients presenting late obstetric complications and during the study of genitourinary malformations (Medina *et al*., 2015).

Diagnosis

Imaging techniques are essential for the diagnosis, treatment and reproductive counseling in patients with paramesonephric duct anomalies. The medical evaluation

Table I. Development phase of the paramesonephric duct and its correlation with uterine anomalies.

Phases of development of the paramesonephric duct	Defect	Anomaly
Development of the paramesonephric duct: -Between both paramesonephric ducts initially and later between fused ducts and the urogenital sinus (senovaginal bulb).	- Bilateral development failure.	-Aplasia/Agenesis. (*MRKH)
	-Unilateral developmental failure.	-Unicornuate uterus.
-Fusion or Unification.	-Horizontal fusion defect.	-Didelphous uterus/bicornuate uterus
	-Vertical fusion defect.	-Transverse vaginal septum/inperforated hymen.
Septal resorption or canalization.	-Defect in resorption or channeling.	-Septate uterus -Arcuatus

of the internal and external contours of the uterus is key to establishing a diagnosis and correctly classifying a uterine anomaly (Jayaprakasan & Ojha, 2022). However, this requires diagnostic confirmation with invasive methods, such as hysteroscopy and diagnostic laparoscopy. Fortunately, other non-invasive tests are currently available that allow diagnosis through images with a high rate of sensitivity and specificity, highlighting the use of abdominal/pelvic MRI, as well as 3D transvaginal ultrasound, presenting a series of advantages and disadvantages which are summarized in Table I.

Treatment

The management of CUD should be evaluated on a case-by-case basis. It is also worth mentioning that they are not always resolved through surgical approaches. Some patients would benefit from hormone suppression treatment or management with contraceptives administration to block menstruation. In other cases where pelvic pain is present or there is family planning that requires fertility, patients should be referred for specialist management.

The Unicornuate Uterus only needs surgical correction in cases where a cavitated rudimentary non-communicating uterine horn is present, in which case resection is necessary due to the resulting pain from the impediment of menstrual flow. In some cases, the uterine muscle mass is reduced, causing isthmo-cervical incompetence, and there may also be a need for cerclage in a future pregnancy (Letterie *et al*., 2011).

The Didelphys Uterus malformation has a good reproductive prognosis and only requires intervention in cases of OHVIRA syndrome, since one of the vaginas is obliterated and it is necessary to resect the septum between them to drain the hematocolpos and hematometra, thus allowing the normal output of menstrual flow (Kapczuk *et al*., 2018).

The Bicornuate Uterus is not associated with infertility, but rather with recurrent miscarriage occurring in the second trimester of pregnancy or premature birth. When no other cause is identified, surgery is recommended, with good results and a pregnancy rate of 90% (Papp *et al*., 2006).

The Septate Uterus is the most common malformation, presenting the worst prognosis for reproduction, since it is associated with spontaneous abortion during the first or second trimester of pregnancy. In the past, it was believed that septal resection was the standard management to improve outcomes in relation to pregnancy, abortion, and premature birth rates. However, more recently it has been demonstrated that septal resection by hysteroresectoscopy does not improve live birth or fertility rates in women with a septate uterus (Riken *et al*., 2021).

CONCLUSIONS

Most paramesonephric disorders (CUD) primarily affect the uterus. These are usually manifested in adolescence, accompanied by symptoms of pelvic pain and primary amenorrhea, but they can also be asymptomatic, with incidental diagnosis in patients undergoing infertility studies. It is always important to consider its embryological origin, since there is a strong correlation with kidney anomalies. Although CUD are described in detail in many classification systems for paramesonephric anomalies, a perfect classification does not exist, probably due to the great complexity of some less common forms. Although strong evidence of genetic causality has been documented, their origin is not yet fully resolved.

Its diagnosis must be performed through the use of imaging techniques, highlighting among them the use of abdominal and pelvic resonance or 3D transvaginal gynecological ultrasound. Possible associated renal alterations must always be kept in mind, for a targeted search with the use of images, also considering the embryological origin of these anomalies. Finally, it is necessary to point out that clinical management is not standardized as it will depend on the age of the patient, the hospital or clinic, and their family planning intentions.

P**IZARRO, P.; RALPH, C.; ROA, I. & ROJAS, M.** Malformaciones congénitas uterinas. *Int. J. Morphol., 43(3)*:941-947, 2025.

RESUMEN: Las Malformaciones Congénitas Uterinas (CUD) son, por lo general, asintomáticas, benignas y de diagnóstico incidental. Con el propósito de describir los diferentes tipos de CUD, es necesario entender su desarrollo embrionario, enfatizando al mismo tiempo la importancia de los conductos paramesonéfricos, estructuras que posteriormente en el desarrollo darán lugar a las tubas uterinas y al conducto útero-vaginal. Los objetivos del presente estudio fueron analizar aspectos básicos del desarrollo normal y patológico del tracto genital femenino durante el desarrollo embrionario/fetal, correlacionándolos con la evaluación histológica, y relacionar tales aspectos con posibles futuras patologías uterinas que las niñas podrían llegar a experimentar desde el inicio de la pubertad. Se estudió un feto humano de aproximadamente 8 semanas de gestación. También se utilizaron como modelo animal 4 fetos de ratón de 15 días post coito, de los cuales 2 correspondieron a individuos hembras y 2 a individuos machos. Las muestras se fijaron en Formalina al 10% y posteriormente fueron procesadas mediante técnica histológica de rutina y tinción con el colorante Hematoxilina- Eosina. La mayoría de las malformaciones paramesonéfricas afectan principalmente al útero, y se caracterizan por la manifestación de déficits, ya sea en el desarrollo, la fusión o la canalización de los conductos paramesonéfricos. Diversos mecanismos de desarrollo, tales como la proliferación celular, apoptosis y las transformaciones epitelio-mesenquimáticas, son

fundamentales para el normal desarrollo de las tubas uterinas y del útero. Las malformaciones paramesonéfricas se manifiestan generalmente durante la adolescencia, y se suelen presentar acompañadas de síntomas entre los que cabe mencionar el dolor pélvico y la amenorrea primaria.

PALABRAS CLAVE: Conducto paramesonéfrico; Malformaciones congénitas uterinas; Anomalías Mullerianas.

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