Review Article ISSN 2835-6276

American Journal of Medical and Clinical Research & Reviews

Genital Malformations and Genetic Errors

Mauri José Piazza, MD

I Tocogynecology Department, Universidade Federal do Paraná – UFPR – Curitiba (PR), Brazil

*Correspondence: Mauri José Piazza, MD

Received:25 May 2025; Accepted:05 June 2025;Published:15 June 2025

Citation: Mauri José Piazza. Genital Malformations and Genetic Errors. AJMCRR. 2025; 4(6): 1-11.

Abstract

The aim of this study is to review the genic or chromosomal abnormalities involved in the development of Müllerian or gynecological malformations.

The frequency of congenital anomalies in the female genital tract ranges from 0.1% to 3.0% of live births. This study aims to characterize the potential chromosomal and genetic anomalies involved in the triggering phenomena.

Keywords: genetic abnormalities, urogenital abnormalities, genital malformations.

Introduction

Human sexual differentiation is a coordinated process following a sequence of events that occur from conception. This sequence of events is dependent on chromosomal-genic and harmonic hormonal factors leading to a perfect organogenesis.

These events are molecular phenomena that will induce, in the female fetus with 46,XX chromosomal pattern or similar, a perfect development of the ovarian structures, Müllerian structures and external genitals (1) (2).

Male differentiation will occur progressively, with the initial stimulus for the development of the testicles, followed by the mesonephric structures, also known as Wolffian structures, and the external genitals by the action of fetal androgens.

The initial stimulus for the testicular development is by the expression of the SRY gene (sex determining region Y gene) which is located on the short arm of the Y chromosome that will determine the development of the testicles (3). Several SRY gene mutations have caused abnormalities in sexual differentiation in 46,XY individuals (4).

Female sexual differentiation is less known under the gene aspect, as observational models express that ovarian development occurs by the absence of SYR gene expression, while the development of Müllerian paramesonephric structures occurs due to the absence of MIF (Müllerian inhibition factor) gene expression, and its testicular production results from Sertoli cells. Given the wide diversity of genital anomalies, whether resulting from ovarian or Mullerian structures, these are believed to be caused by abnormalities in several genes.

Embriology

The female reproductive system is composed of the gonads (ovaries), internal structures developed from the Müllerian ducts (including the uterus and vagina) and external genitalia (vulva and its components). The gonads develop from the genital ridges that are formed by the thickening of the coelom and by the germ cells that migrate in the sixth pregnancy week.

The embryological origin of the Müllerian ducts shows, from the fifth-sixth week of pregnancy, that they are originated from the mesoderm while the urogenital sinus originates from the endoderm.

In the sixth week of embryo life, still during the undifferentiated phase, both male and female embryos have 2 pairs of structures, named the Wolffian and Müllerian ducts (5). In female embryos, in the absence of fetal testosterone and the inhibiting factor of Müllerian structures, occurs the involution of Wolffian structures. The Müllerian ducts originate from invaginations of the coelomic epithelium, located on the anterolateral surface of the urogenital ridge. Longitudinally located in the embryo, these structures undergo an elongation process around the ninth week of gestation, when 3 distinct regions are identified: cranial, horizontal vertical and vertical-caudal.

The most cranial and upper portion is opened; they are separated and give origin to the fimbriae of the fallopian tubes. The horizontal portion migrates and extends laterally to the Wolffian ducts, later progressing in the craniocaudal direction. The remaining part of the fallopian tubes is formed, while the caudal-vertical portions are initially separated by a septum, but these structures will merge and form the uterovaginal primordium.

As for the fusion of the Müllerian ducts, it occurs in the craniocaudal direction and potential anomalies may occur such as uterine septum, double uterine cervix and longitudinal vaginal septum.

The uterovaginal primordium is comprised of two distinct parts: the uterine region and the upper third vaginal canal. In the initial phase, the uterus is shaped like a bicornuate uterus, but around the twelfth week of intrauterine life, its volume increases in the bottom resulting in a piriform shape. The endometrium is derived from the fusion line of the Müllerian ducts while the endometrial stroma and the myometrium will be derived from the adjacent mesenchyme. This entire process of uterine development will be complete in the twentieth second week of gestation (5).

The fusion of the Müllerian structures with the urogenital sinus must occur for the development of the vagina. Thus, the caudal portion of the uterovaginal primordium will insert into the dorsal portion of the urogenital sinus, forming the Müllerian tubercle or Müllerian sinus. This tubercle induces the formation of the vaginal plaque portion, which is tubular in shape, and this channeling is completed around the twentieth week of gestation.

The epithelium of the upper 1/3 of vagina is believed to originate from the uterovaginal primordium, and the lower 2/3, from the urogenital sinus.

The hymen in turn, is a vestige of the endodermal membrane that differs from the vaginal vestibule. Its opening usually occurs around the final period of gestation, being a very thin membrane.

Classifications:

Gonadal (ovarian) anomalies and/or Streak Gonads.

These entities are more frequently found, and we can differentiate them into: Gonadal Dysgenesis and Primary Ovarian Insufficiency or Premature Ovarian Failure.

Female Gonadal Dysgenesis comprises 3 distinct entities where no gonadal differentiation occurred, and only the streak gonads persist originating from the germ ridges without germ cells within them.

Among them:

Gonadosomatic dysgenesis (Turner Syndrome) is the most frequent female chromosomal abnormality occurring on 1:2500 female fetuses. It is a chromosomal abnormality known as monosomy X or 45,X (6), although other abnormalities with different chromosomal patterns such as 45,X/46,XX, isochromosome X (Xq isochromosome) or ring X may be found. Turner syndrome can present numerous somatic stigmas such as short stature, webbed neck, cubitus valgus and cardiac anomalies.

Pure Gonadal Dysgenesis characterizes patients with genetic pattern 46,XX or 46,XY (Swyer Syndrome) (7) where the dysgenetic gonads are not accompanied by somatic stigmata, being carriers of Primary Amenorrhea with high levels of pituitary gonadotropins. The internal and external genitals are normal with hypotrophy.

Gonadal dysgenesis can occur as part of Perrault's syndrome accompanied by deafness with or without cerebellar ataxia (8). Its etiology is unknown, although several gene mutations were evidenced in the FSHR, BMP15 (Xp11.2) and NR5A (9q33) genes.

Asymmetric or Mixed Gonadal Dysgenesis occurs due to a mitotic error of a single zygote with a genetic pattern of 45X/46XY (9). In the evaluation of the gonads, on one side, there are streak gonads and, on the other side, an immature testicle. In these individuals there may be, on one side, Müllerian structures while the other carries Wolffian structures.

Primary Ovarian Insufficiency or Premature Ovarian Failure

It is characterized by the ovarian insufficiency before the age of 40 and is considered as a condition of Hypergonadotropic Hypogonadism with early secondary amenorrhea. Clinical manifestations occur due to progressive estrogen deficiency with vasomotor phenomena (hot flushes and night sweat) and genital hypotrophy and atrophy in consequence of estrogen deficiency. Among the possible causes of ovarian failure, there are genetic diseases such as fragile X syndrome and Turner syndrome, both presenting a deficiency in the number of follicles; autoimmune diseases such as thyroiditis, Addison's disease, rheumatoid arthritis and metabolic diseases, as well galactosemia, post radiotherapy and chemotherapy and/or exogenous toxins.

TABLE 1

SITES OF GENE ALTERATIONS ON X CHROMOSOME IN OVARIAN INSUFFICIENCY 1a

Gene	Gene error sites
Fop2	Xq13-3 to Xq22 ovarian failure between 16-21 years of age
FMR1	Xq27.3 (Deletion in the long arm of the X chromosome on the Xq13-25 region). X fragile syndrome With intellectual disability (Translocations on the Xq13-26 region)
FMR2	Xq28 – clinical condition similar to FMR1
BMP15	Xp11.2 – mutation of the follicular morphogenetic protein gene Oocytes – no oocyte response

POSSIBLE SITES OF AUTOSOMAL GENES LINKED TO PRIMARY OVARIAN INSUFFI-

CIENCY

Gene	Damage	Error sites
ATM	Ataxia/telangiectasia mutated	11q22-3
POLG	Polymerase (DNA directed) Y	15q25
BLM	RecQ Protein like 3-DNA helicase	15q26-1
AIRE	Autoimmune regulator polyglandular failure type 1	21q22-3
EIF2B-2	Eucaryotic translation initiation factor 2B-subunit2	14q24
EIF2B-4	Eucaryotic translation initiation factor 2B-subunit4	2p23
EIF2B-5	5 Eucaryotic translation initiation factor 2B-subunit5	3q27

TABLE 2

Müllerian Anomalies

Among all the classifications of genital anomalies, the one proposed by Buttram and Gibbons (11), later accepted by the American Fertility Society (12), today so-called the American Society of Reproductive Medicine.

Class	Types of Anomalies	
1.	Agenesis-Hypoplasia (Uterus-vaginal)	Tuba Uterine body Cervix Vagina Associated
2.	Unicornuate Uterus accessory horn with cavity cavity - solid	Single horn Rudimentary no
3.	Uterus Didelphys vaginal septum nal septum syndrome)	Longitudinal Oblique vagi- (Wunderlich
4.	Bicornuate Uterus	Complete Partial
5.	Septate uterus	Complete Partial
6.	Arcuate uterus	
7.	Abnormalities induced by DES (Diethylstilbestrol)	

General Considerations

Most congenital anomalies in the female genital tract are of unknown etiology and many of these patients are considered isolated cases, however some conditions are present in members of the same family.

Thus, these anomalies have their own characteristics while genetic and environmental factors may favor their occurrence. The simultaneous occurrence of Müllerian abnormalities associated with defects in other organs has shown that these conditions are simultaneously related to genetic factors.

Among these anomalies are found:

HOXA 13

Hand-foot-uterus syndrome is an autosomal dominant genetic disease, where multiple skeletal anomalies are also described, mainly found in the hands and feet, and several types of anomalies in the fusion of Müllerian structures. Genital duplicity may present a wide anatomical variety and Mortlock and Innis (13) described its casual factor as a mutation of the HOXA 13 gene. The HOXA 13 gene is located on the short arm of chromosome 7, between the positions of loci 14 and 15. In this eventuality, several mutations have been described, 40% are reported as gene point mutations while 60% are referred to as polyamine expansion. Multiple phenotypic manifestations may also be present, with uterine fusion anomalies, suggesting that the expression of other genes would be relevant for its perfect development.

The genes of the HOXA family are essential for determining the development of Müllerian structures. The expression of the HOXA 9 gene is relevant in the development of the fallopian tubes, HOXA 10 facilitates the development of the uterus,

HOXA 11 is essential for the development of the lower segment of the uterus and cervix, while HOXA 13 helps in the development of the ectocervix and the upper third of the vagina (14) (15). HOXA 10 and HOXA 11 are also expressed in the endometrium during its proliferative phase, being increased during the secretory phase of the endometrial cycle (16).

Fragile X Genetic Mutation

It is a gene mutation found on X chromosome determined by paternal characteristics and the X-linked dominant (17). It is more frequent in men, presenting many possible clinical manifestations. Women present a milder clinical condition, as they have double XX and the gene of the other X chromosome. Fragile X syndrome is also associated with ataxia/tremors including memory loss and/or intellectual disability, there may also be numbness in the hands and feet. A fertility decline is commonly reported associated with early ovarian failure.

Like other causal factors, several gene errors may be associated, such as partial deletions on the X chromosome or translocations of chromosomal fragments. They are caused by inactivation of the FMR1 gene (Fragile X intellectual disability) located on the X chromosome long arm, with a constriction of its long arm (Xq27.3 or Xq13-25) (18).

Cystic fibrosis transmembrane conductance regulator (CFTR)

CFTR gene mutation is a genetic disease of major lethality that may cause cystic fibrosis. It may occur in result of a wide variety of genetic mutations capable of causing disorders of different phenotypes. In this case, patients may have severe respiratory disorders or pancreatic deficiency or, sometimes, be asymptomatic.

Among men, there may be Wolffian structures anomalies such as agenesis of the vans deferens. CFTR gene mutations (19) have also been correlated with inadequate development of Müllerian structures.

Wilms Tumor (WT 1)

This gene is named after Wilms nephroblastoma which is an intra-abdominal solid tumor frequent in children with an incidence of 1:10000 newborns. This gene is located on chromosome 11p13 and has been deleted in patients presenting this neoplasia, accompanied by intellectual disability, genital malformations and hypoplasia or agenesis of the iris (20).

These mutations have been evidenced in patients with Denys-Drash Syndrome (21) and male patients may present urogenital abnormalities such as male pseudohermaphroditism. Early WT1 gene manifestation is necessary for the development of Müllerian structures. Mutations in this gene will result in an inappropriate action of the Müllerian duct inhibitor factor, causing a partial regression of the Müllerian Ducts.

Mullerian inhibiting substance (MIS/AMHR)

Deficiency or absence of the MIS receptor may result in persisting Müllerian ducts in men, while their inappropriate gene expression can lead to abnormal regression of Muller's ducts such as uterovaginal agenesis or other uterine anomalies.

The Anti-Mullerian hormone (AMH) / Mullerian inhibiting substance (MIS) gene is located on chromosome 19q13.2-13.3 and can encode a glycoprotein that is produced in the Sertoli cells of male fe-

tuses. In this way, they induce the regression of Müllerian structures, while in female fetuses, their existence may induce a decrease in aromatase activity in ovarian granulosa cells (22) (23).

TRIPLE XXX or TRIPLE X SYNDROME

It is a frequent chromosomal anomaly in women with a 47,XXX pattern, succeeding a non-disjunction of the X chromosomes, with a wide variety of potential clinical manifestations. They are often asymptomatic, and others have delayed psychomotor development with cognitive deficit. In childhood there may be delayed motor development and anomalies in the reproductive system with a low fertility rate and progressive ovarian failure (24). X trisomy may be due to a deletion of the X (Xp) short arm or in the Xq13-25 region of the X long arm. Less frequently, it was evidenced the translocation of part of the X chromosome in the Xq 13-26 region (25).

ANOMALIES OF THE INTERNAL AND EXTERNAL GENITALS

Absence of the Uterus and Vagina

The etiology of Müllerian agenesis is not defined due to a great variability of anomalies that are likely to occur. Many cases occur sporadically, although several familial situations were recently described, which may involve genetic factors. The karyotype of these patients is 46,XX and around 4% is related to familial occurrence.

Müllerian agenesis has also been associated with enzymatic errors of galactose-1-phosphate-uridyltransferase (GALT) and excessive exposure to galactose which would be considered responsible for the abnormal vaginal development (26).

Other citations refer to mutations in the gene and receptors of the anti-müllerian hormone or in the substance that inhibits Müllerian structures as responsible for these anomalies.

Another possible cause for the anomalies in the fallopian tubes, uterus or uterine cervix and in the upper 1/3 of the vagina is the loss of function due to WNT4 gene mutation (26) or modifications of the HOXA 9 and HOXA 13 genes (13). The genes of the WNT family are known to be responsible for interactions between epithelia and mesenchyme. WNT4 gene encodes a growth factor that induces the development of kidneys, adrenals, breasts, pituitary gland and reproductive system.

WNT5A plays an important role in the regulation of the uterine stroma and in the epithelial development of the uterine glands, as well as in a better response of the uterus to exogenous estrogens (27).

WNT7 is essential for the development of the Müllerian ducts, whereas WNT9 is expressed in the epithelium of the Wolffian ducts in both men and women (28).

In recent years, these patients have been surgically treated using different techniques to correct this anomaly. The aim is to obtain a vagina with convenient depth and a trophic vaginal mucosa, using several tissues such as skin or amniotic membrane (29).

Fusion defects of Müllerian structures

These fusion defects of Müllerian structures comprise a wide range of clinical manifestations being characterized in II, III, IV, V of the AFS/ASRM classification.

Among these anomalies, the hand-foot-uterus syn-

drome is an autosomal dominant disease previously described and other fusion defects are characterized as being of polygenic or multifactorial etiology, such as those included in trisomy 13 and 18, in the syndrome described by Meckel-Fraser-Robert, and in Bardet-Biedl syndrome (30).

Persistence of the longitudinal vaginal septum

The persistence of the longitudinal vaginal septum is due to an incomplete reabsorption of the septum which is formed during the fusion of Müllerian structures. Its permanence may be associated with defects in uterine fusion and this septal defect is due to the proliferation and mesoderm persistence.

Two genetic syndromes associated with this malformation have been described as Edwards-Gale syndrome (31), which is an autosomal dominant syndrome, and Johanson-Blizzard syndrome (32), a rare autosomal recessive disorder.

Persistence of the transverse vaginal septum

Sporadic disorder of unknown etiology. However, in McKusik-Kaufman syndrome it is associated with polydactyly, a congenital heart disease with higher incidence in the Amish community. The transverse vaginal septum may also be identified. It is described as an autosomal dominant disease. The genetic locus responsible for this syndrome is located specifically at locus 20p.12 (33), on chromosome 20.

Imperforate Hymen

It is a condition occurring sporadically, affecting around 0,1% of female newborns. It may occur in certain families and was described in patients with ulnar-mammary syndrome where there is hypoplasia / aplasia of breasts growth and the coexistence of hymen imperforation and skeletal and apocrine glands anomalies. Mutations of the TBX3 gene were detected, a protein transcription factor (34). This gene is located on the long arm of chromosome 12.

External genital anomalies

The fusion of labia minora is a very common abnormal disorder, suggested causes are enzymatic errors of the adrenals with excessive production of androgens and also the association with hypoestrogenic states.

Clitoris hypertrophy may rarely occur in association with Donahue's syndromes (35) and Beckwith -Wiedemann syndrome (36) (37).

Anomalies caused by environmental and hormonal factors

The sporadic occurrence of several structural anomalies in the female genital tract also suggests that exposure to certain teratogenic agents may be their causing factor. Among them, 2 causal agents may act as inducing agents such as thalidomide and diethylstilbestrol. Thalidomide is a teratogenic agent that induces defects in the mesoderm and consequent anomalies in the limbs, urinary tract, circulatory system and heart (38). Phocomelia will be present in 100% of these cases and a third of these patients will have anomalies in the genital tract such as fusion defects, which may vary from genital agenesis to bicornuate uterus and/or longitudinal septa.

In this eventuality, thalidomide may have an effect, disrupting the expression of genes that are important for the normal development of the genital tract.

Diethylstilbestrol (DES) is a synthetic non-

steroidal estrogen widely used in the past for the prevention of recurrent miscarriages and preeclampsia. However, it was found that the daughters of patients using DES began to develop higher rates of vaginal adenosis and clear cell adenocarcinoma (39). In the same group of patients, there was a higher occurrence of uterine anomalies, characterized as T-shaped uterus, in approximately 68% of the patients (39) (40) and other anomalies, such as uterine hypoplasia, abnormalities in the fallopian tubes and cervix.

The exact mechanism of DES's teratogenic effect is still unknown, although it is believed to interfere with, inducing changes in the expression of one or more genes of the HOX family, especially the HOXA 10 and HOXA 11 genes. It would be the same abnormality found in the HOXA 13 gene expression detected in patients with hand-foot-uterus syndrome (13).

Galactosemia is an autosomal recessive syndrome where there is an inability to convert galactose into glucose due to an enzymatic deficiency and consequent accumulation of metabolites in various organs including the ovaries, consequently leading to ovarian failure and early ovarian failure. The GALT gene is located on chromosome 9p13 and GALK gene on chromosome 17q24, while GALE gene is located on chromosome 1p36 (26).

Several Syndromes related to Genital Malformations with Different Genes (41):

Syndrome	Anomalies
Beckwith-Wiedemann	Clitoromegaly and Fetal Hypergrowth with Macroglossia and Embryonal Tumors/ Autosomal Dominant Anomaly Error located on chromosome 11p15.5-BWR1A gene
Donahue's	Clitoromegaly and Short Stature Reduced Insulin Receptors with Insulin Resistance and Acanthosis Nigricans Autosomal recessive mutation with INSR Gene Mutation of chromosome 19 - 19p13.2 (Leprechaunism)
Robert's	Clitoromegaly and multiple abnormalities (Pseudothalomide) It is an Autosomal recessive mutation on chromosome 8 - ESCO 2 gene
Robinow's	Hypoplasia of the External Genitals – Dwarfism with short limbs/Vaginal atresia. Autosomal recessive mutation with error on chromosome 9 ROR 2 gene – position 9 on the long arm of Cr9
Pterygium	Hypoplasia of the labia and clitoris. Autosomal Recessive
Ulnar-mamaria	Imperfurate Hymem. Autosomal recessive TBX3 mutation
McKusick-Kaufman	Transverse Vaginal Septum/ Chondrodysplasia/Heart Diseases Autosomal recessive mutation associated with MKKS Cr 20 protein
Langer-Giedion	Transverse Vaginal Septum/Short Stature/Facial Dimorphism Trichorhinophalangeal syndrome/Intellectual disability/Microcephaly Autosomal dominant – deletion on chromosome Cr 8q24.1 TRPS1 e EXT1 Genes
Edwards-Gale	Longitudinal Septum – Low Birth Weight – Microcephaly and Developmental Delay – Autosomal Dominant Extra chromosome 18 with trisomy 18
Meckel's	Longitudinal Septum – Dysencephalia splanchno cystica –Cleft Palate – Autosomal Recessive – Potential errors in chromosomes: 17q21-24 (MKS1), 11q13(MKS2), 8q21.3-22.1(MKS3), 12q21.31-q21.33(MKS4), 16q12.2(MK55), 4p15.3(MK56)
Johanson-Blizard	Longitudinal Septum – Skull Facial Anomalies – Cleft palate Autosomal Recessive 1 or more mutations of the VBR1 gene
Waardenburg type 2	Vaginal atresia – Skeletal abnormalities – skin, hair, eyes, iris color alteration Reduced hearing Autosomal dominant Several genetic mutations: EDN3-EDNRB-MITF-PAX3-SNA12-SOX10-
Hand-foot-uterus	Autosomal Dominant Fusion Defect HOXA 13
Fraser	Fusion Defect with Genital Anomalies - Micropenis

	Clitoromegaly – Ambiguous Genitalia – Cryptophthalmos Autosomal recessive disorder Altered genes – FREM2 GRIP 1 – FRAS 1
Meckel's	Fusion Defect with high lethality – Liver injuries and nervous system with Encephalocele / Cleft Palate Polycystic Kidneys – Polydactyly – Genital Anomalies Autosomal recessive
Bardet-Biedl	Fusion Defect – Hypogonadism – Hyperphagia – Obesity Situs Inversus – Altered Gene Expressions: BBS1- BBS2 - BBS3, etc. Autosomal Recessive

CONCLUSION

The multiplicity of genital anomalies, whether of chromosomic/genetic origin due to epigenetic factors, require extensive knowledge about potential malformations in different age groups. Medical guidance and appropriate laboratorial exams with satisfactory lab results, is essential to implement the necessary corrections allowing that these patients enjoy living a regular life to the fullest, or as closely as they can.

Reference:

1. Acien P. Embryological observations on the female genital tract. Hum Reprod 1992;7 (4):437-45
2. Persaud TN. Embriology of the female genital tract and gonads. In: Copeland IJ,Jarrell J, McGregor Y eds. Textbook of Gynecology. Philadelphia, Pa. WB Saunders 1993;321
3. Kashimada K, Koopman P. SRY: the master switch in mammalian sex determination. Development 2010;137(23)3921-30 PIMD 21062860
4. Sinclair AH, Berta P, Palmer MS, Hawkins JR, Griffiths BL, Smith MJ et al. A gene from the human-sex-determining region encode a protein with homology to a conserved DNA biding motif.Nature 1990;346:240-244
5. Moore KL, Persaud TN. The urogenital system: the development of the genital system. In: The Developing Human: Clinically oriented Embriology. Philadelphia Pa. WB Saunders 2003;287
6. Palmer CG, Reichman A.Chromosomal and clinical findings in110females with Turner syndrome.Hum Genet 1976;35:35-42
7. Michala L, Goswami D, Creighton SM, Conway GS. Sindrome de Swyer: apresentação e desfechos. BJOG 2008;115:737-41
8. Demain LA, Urquart JE, O'Sulivan J, Williams SG, Bhaskar SS, Jemkinson EM, Lourenço CM et al. Expandindo o espectro genotipico da syndrome de Perrault. Clin Genet 2017;91:302-12
9. Alvarez-Nava F, Gonzalez S, Soto S, Pineda L, Morales-Machin A. Mixed Gonadal dysgenesis:a syndrome of broad clinical, cytogenetic and histopathologic spectrum. Genet Couns 1999;10:233-43
10. Fortuno C, Labarta E. Genética da insuficiência ovariana primária:uma revisão. J Assist Reprod Genet 2014;31(12):1573-1585
11. Buttram VC Jr, Gibbons WE. Mullerian anomalies:a proposed classification.An analysis of 144 cases. Fertil Steril 1979;32(1):40-6
12. The American Fertility Society classifications of adnexal adhesions, distal tubal occlusion, tubal occlusion secondary to tubal ligation, tubal pregnancies, mullerian anomalies and intrauterine adhesions. Fertil Steril 1988;49(6):944-55
13. Mortlock DP, Innis JW. Mutations of HOXA 13 in hand-foot-genital syndrome. Nature Genet 1997;15:179-80
14. Goodman FR. Limb malformations and the human HOX genes. Am J Med Genet 2002;112:256-65

15. Lahwani S, Wu HH, Reindollar RH et al. HOXA 10 mutations in congenital absence of uterus and vagina. Fertil Steril 2008;89:325-30
16. Du H, Taylor HS. Molecular regulation of Mullerian development by HOX genes. Ann NY Acad Sci 2004;1034:152-65
17. De Vries BBA,van den Onwelan AMW, Mobikaamsing S. Scanning and diagnosis for the fragile syndrome among the mentally retarded:am epidemiological and psychological survey. Am J Hum Genet 1997;61:660-667
18. Turner G,Webbt T, Wake S, Robinson H.Prevalence of fragile syndrome 1996;64:196-197
19. Dork T, Dworniczak B, Aulehla-Scholz C et al. Distinct spectrum of CFTR gene-mutations in congenital absence of vas deferens. Hum Genet 1997;100:365-77
20. Reddy JC, Licht JD. The WT1 Wilms' tumor suppressor gene:how much do we really know? Biochim Biophys Acta 1996;1287:1-28
21. Baird PN, Santos A, Groves N, Jadresic L, Cowell JK. Constitutional mutations in the WT1 gene in patients with Denys-Drash syndrome. Hum Mol Genet 1992;1:301-05
22. Rey R. Anti-Mullerian hormone in disorders of sex determination and differentiation. Arq Bras Endocrinol Metabol 2005; 49:26-36
23. Tiker F, Yildirim SV, Barutcu O, Bagis T. Familial mullerian agenesis. Turk J Pediatr 2000; 42(4):322-4
24. Wigby K, D' Epagnier C, Howell S,Reicks A, Wilson R, Cordeiro L, Tartaglia N. Expanding the phenotype of Triple X syndrome:a comparison of prenatal versus postnatal diagnosis. Am J Med Genet 2016;170:2870-2881
25. Goswani R,Goswani D,Kabra M, Gupta N, Dubey S, Dadhval V. Prevalence of the triple X syndrome in phennotipically normal women with premature ovarian failure and its association with autoimune thyroid disorders. Fertil Steril 2003;80:1052-1054
26. Klipstein S, Bhagavath B, Topipat C, Sasur L, Reindollar RH, Gray MR. The N314D polymorphism of the GALT gene is not associated with congenital absence of the uterus and vagina. Mol Hum Reprod 2003;9(3):171-4
27. Mericskay M, Kitajewski J, Sassoon D. Wnt5a is required for proper epithelial-mesencymal interactions in the uterus. Development 2004;131:2061-72
28. Carta L, Sassoon D. Wnt7a is a suppressor of cell death in the female reproductive tract and is required for postnatal and estrogen-mediated growth. Biol Reprod 2004;71:444-54
29. Piazza MJ. Study and evaluation of neovagina epithelium. JBRA(Jornal Brasileiro de Reprodução Assistida) 2021;25(9);581-585
30. Stoler JM, Herrin JT, Holmes LB. Genital abnormalities in females with Bardet-Biedl syndrome. Am J Med Genet 1995;55:276-78
31. Edwards JA, Gale RP. Camptobrachydactily:a new autosomal dominant trait with two probable homozygotes .Am J Hum Genet 1972;24:464
32. Johanson A, Blizzard R. A syndrome of congenital aplasia of the alae nasi,deafness,hypothyroidism,dwarfism,absent permanent teeth and malabsorption. J Pediatr 1971; 79:982
33. Adam A, Hellig J, Mahomed N,Lambie L.Recurrent urinary tract infections in a female child with polydactyly and a pelvic mass: consider the McKusick-Kaufman syndrome. Urology 2017;103:224-225
34. Zlotina A, Kiselev A, Serguschichev A, Parmon E,Kostareva A. Rare case of ulnar-mammary syndrome with lelft ventricular tach-

ycardiua and lack TBX3 mutation. Front Genet 2018;9:209
35. Donohue WL, Uchida IA. Leprechaunism: a euphemism for a rare familial disorder. J Pediatr 1954;45:505-19
36. Choufani S, Shuman C, Weksberg R.Sindrom de Beckwith-Wiedeman . J Med Genet.Seminar Med Genet 2010;154C:343-54
37. Choufani S, Shuman C, Weksberg R.Achados moleculares na syndrome de Berckwith-Wiedeman. Am J Med Genet-SeminarMed Genete 2013;163C:131-40
38. Takumi I, Hideki A, Takayuki S, Toshihiko O, Kentaro O, Yoshimasa I et al. Identification of a primary target of thalidomide teratogenicity. Science 2010;327:1345-1350
39. Mittendorf R. Teratogen update:carcinogenesis and teratogenesis associated with exposure to diethylstilbestrol(DES) in utero. Teratology 1995;51:435-45
40. Senekjian EK, Potkul RK, Frey K, Herbst AL. Infertility among daughters either exposed or not exposed to diethylstilbestrol. Am J Obstet Gynecol 1988;158:493-98
41. Christopoulos P, Gazouli M, Fotopoulou G, Creatsas G. The role of genes in the development of Mullerian anomalies. Where are we today? Obst Gynecol Sur 2009;64(11):760-68