SBUS SOCIEDADE BRASILEIRA DE ULTRASSONOGRAFIA

DOI: 10.29327/218041.32.37-1

ISSN 2675-4800

SCIENTIFIC ARTICLE - CASE REPORT

UNRAVELING MIXED GONADAL DYSGENESIS: CHALLENGES IN PRENATAL DIAGNOSIS AND CLINICAL MANAGEMENT

EDUARDO DE FREITAS KELSCH [1], MIRIAN FRANCINE FAVERO [1], THIAGO MENEZES CÉZAR [1], ISABELLA KAPCZINSKI MÜLLER [1], JORGE ALBERTO BIANCHI TELLES [2], RAFAEL FABIANO MACHADO ROSA [1]

1- UFCSPA Porto Alegre-RS
2- Serviço de Medicina Fetal (HMIPV) -Porto Alegre-RS

ABSTRACT

OBJECTIVE: The aim of this study is to report a case of mixed gonadal dysgenesis (MGD) diagnosed during pregnancy, highlighting the importance of prenatal diagnosis, clinical management, and genetic counseling.

CASE REPORT: The patient was a 20-year-old woman referred due to a fetal ultrasound showing evidence of renal abnormalities. At the 30-week ultrasound, a dysplastic right kidney with multiple cysts and ambiguous genitalia suggestive of a disorder of sexual development was observed. Fetal magnetic resonance imaging (MRI) revealed a dysplastic kidney with multiple cysts. There was an image suggestive of a hypoplastic scrotum and an undefined genital tubercle. The fetal karyotype showed a chromosomal constitution of mosaicism 45,X[28]/46,XY[2], consistent with the diagnosis of MGD. On neonatal clinical examination of the genitalia, there was a phallus measuring 3 cm with hypospadias but no urethral opening, and a palpable gonad in the left labioscrotal swelling. The right gonad was intra-abdominal, and the urethra opened into a wide urogenital sinus. Micrognathia, a single left palmar crease, clinodactyly of the fifth fingers, and hypoplastic nails were also observed. The abdominal ultrasound showed a right kidney with multiple cysts of varying sizes.

DISCUSSION: MGD is a complex condition that can manifest in various ways. The discussed case highlights the importance of a multidisciplinary approach in the management of gonadal dysgenesis cases, considering not only aesthetic aspects but also the functionality and health of the patient. The choice of gender assignment should be made after careful evaluation and in collaboration with the parents, taking into account emotional and social implications.

CONCLUSION: Early diagnosis and proper follow-up are crucial for the management of MGD. Collaboration between different medical specialties and the involvement of the parents in decision-making are essential to ensure appropriate and informed treatment. This case highlights the need for continuous support and careful planning for the child's future.

KEYWORDS: DISORDERS OF SEXUAL DIFFERENTIATION, MIXED GONADAL DYSGENESIS, PRENATAL DIAGNOSIS, POLYCYSTIC RENAL MALFORMATION, MOSAICISM, GENDER ASSIGNMENT

INTRODUCTION

Prostate ultrasound is commonly requested by doctors for male patients over 40 years old, both for diagnostic and screening purposes. The accurate determination of prostate volume is important for determining the degree of hyperplastic enlargement, the resulting tendency for urinary tract obstruction, and the preferred option for surgical treatment. The literature available for transabdominal prostate ultrasound instructs that the scan should be performed with a full bladder and the transducer tilted 15° towards the feet[1].

An enlarged prostate can result in voiding dysfunction due to static (mechanical) or dynamic (smooth muscles of the bladder neck and prostatic urethra) obstruction. Although classical literature is controversial regarding the direct relationship between prostate size and voiding dysfunction in patients with benign prostatic hyperplasia (BPH) and its implications for management and outcomes, some recent studies have highlighted the role of predominant secondary changes in the bladder in small-sized prostates, including a high bladder neck, increased smooth muscle tone in the bladder neck/prostate, and increased prostatic urethral angle, in contrast to the primary obstructive component in large glands[2].

Therefore, the cause of voiding dysfunction in patients with BPH should be established before undergoing surgery to improve the patient's condition, as management strategies differ in bladder outlet obstruction due to small and large prostates. The assessment of post-void residual urine is considered by many urologists to be an important test in patients with benign prostatic hyperplasia. Residual urine is found more frequently in these patients than in the healthy population. However, it does not always correlate with uroflowmetric findings.

Therefore, the objective of this study is to evaluate if

there is a correlation between prostate volume and post-void residual urine volume.

METHODS

This is a retrospective cross-sectional observational study conducted with male patients using data from January to July 2023. The sample size was determined by temporal convenience, and the data were analyzed using Excel. The research was submitted to the Ethics Committee through the Brazil platform, respecting the ethical principles regulating research in human subjects (resolution 466/12).

The variables related to ultrasound findings were: patient age, prostate weight, and post-void residual urine volume.

For the statistical analysis, the Pearson correlation test was applied, where 1 = perfect correlation; 0.75 = strong correlation; 0.5 = moderate correlation; -0.5 = no correlation. Additionally, the Kolmogorov-Smirnov test and Spearman correlation were used.

For the abdominal prostate ultrasound examination, it is essential to have a full bladder. Patients should drink a large volume of water (5 cups) one hour before the procedure. Once ready, the patient lies down in a supine position, and the transducer is used with gel for visualizing the prostate in the pelvic region. Two measurements are taken with the transducer in the longitudinal plane and one in the transverse plane to calculate the volume (transverse x anteroposterior x longitudinal x 0.52), as shown in figure 1. The initial bladder volume is also calculated in the same way at this time. Afterward, the patient empties their bladder to calculate the post-void residual volume.

The reference values for post-void residual urine (PVR) in the study are: absent (no residue), negligible (0 to 40 ml), moderate (40 to 100 ml), and significant (> 100 ml), as shown in figure 2.

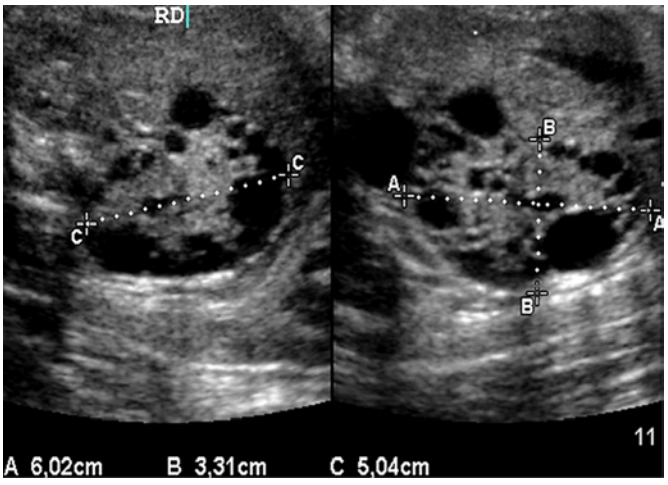


Figure 1: Fetal ultrasound performed at 30 weeks of gestation showing the right kidney (RK) dysplastic with multiple cysts.

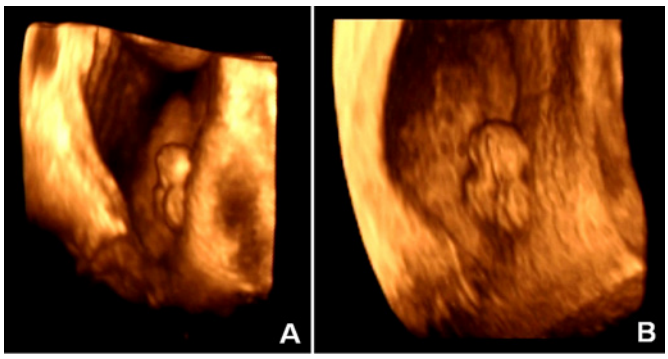
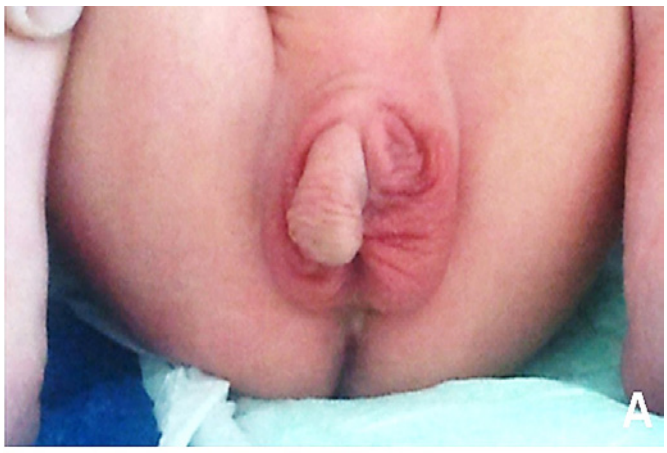


Figure 2: Image obtained through three-dimensional ultrasound showing genital abnormality, suggestive of ambiguous genitalia or a disorder of sexual differentiation (DDS) (A and B).

The supplementary evaluation through fetal magnetic resonance imaging showed an image suggestive of an undefined genital tubercle and an apparent hypoplastic scrotum. The fetal karyotype, obtained through amniocentesis, revealed the presence of a mosaicism 45,X[28]/46,XY[2], which, along with the prenatal findings, indicated the diagnosis of MGD. The fetal echocardiography was normal.

The baby was born at 40 weeks of gestation via cesarean section due to cephalopelvic disproportion, weighing 3180g, measuring 48cm, with a head circumference of 35cm, and Apgar scores of 9 at both the first and fifth minutes. Physical examination revealed the following findings: micrognathia, a single left palmar crease, bilateral clinodactyly of the fifth fingers, hypoplasia of the nails on the hands and feet, and genitalia with a phallus measuring approximately 3 cm with a urethral opening at its base, associated with rough and fused labioscrotal prominences, as well as a palpable left gonad located in the labioscrotal swelling (Figure 3).



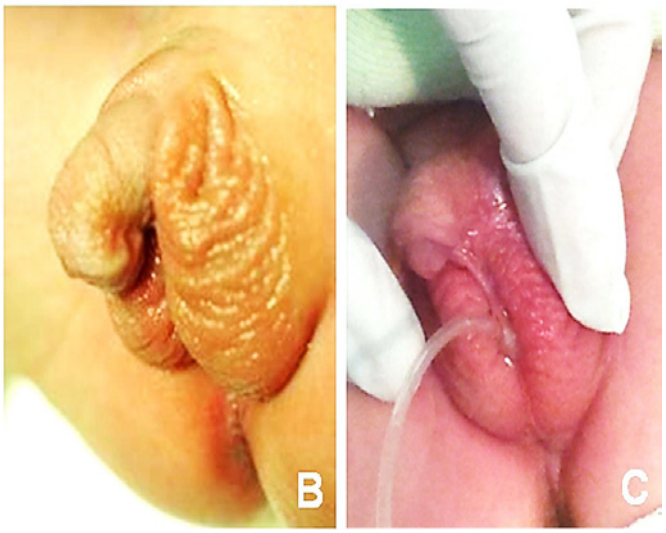


Figure 3: Appearance of the patient's external genitalia observed after birth. Note that the phallus measures approximately 3 cm, with a urethral opening at its base, associated with fused and rough labioscrotal prominences. The urethral catheter indicates the location of the urethral opening.

The right gonad was not located. Upon evaluating the set of findings, the patient's genitalia were classified as Prader stage IV. The Prader scale has five stages, ranging from typical female genitalia to typical male genitalia, with various forms of genital ambiguity in between[3].

Prader Classification[3]:

Grade I: The external genitalia is mostly female with mild clitoral hypertrophy. There is a slight increase in clitoral size, with normal labia and vagina, indicating virilization occurring after 20 weeks of intrauterine life (IUL).

Grade II: More pronounced clitoral hypertrophy. There is slight fusion of the labia, but a separate vaginal opening from the urethra is still visible, indicating virilization starting at 19 weeks of IUL.

Grade III: More complete fusion of the labia majora, forming a "scrotal pouch" appearance. The clitoris is enlarged, resembling a small penis. The urethra and vagina open together into a urogenital sinus, creating a single opening, indicating virilization at [14-15] weeks of IUL.

Grade IV: The clitoris is significantly enlarged, resembling a penis with a single opening for both the urethra and vagina (urogenital sinus). Labial fusion is nearly complete, forming a scrotal-like appearance, but no testicles are present. This degree corresponds to ambiguous genitalia, where it is harder to distinguish between sexes, as the external genitals resemble male genitalia without testes. It indicates virilization at [12-13] weeks of IUL.

Grade V: The external genitalia is completely male, with full fusion of the labia into a scrotal sac and advanced clitoral enlargement so that the organ resembles a penis. There may be a urethral opening at the level of the glans, similar to a typical penis, but the absence of testicles is a distinguishing feature, indicating virilization at [11] weeks of IUL.

The postnatal abdominal ultrasound showed that the right kidney had multiple cysts of varying sizes, with some enlarged. The inguinal ultrasound demonstrated a topical left gonad with a minimal associated hydrocele. The right gonad could not be identified.

The child's hormone levels revealed total testosterone at 0.2 ng/mL, androstenedione at 2.19 ng/mL, and alpha-fetoprotein levels above 300 ng/mL. Abdominal and pelvic video laparoscopy showed the presence of a long urogenital sinus, measuring approximately 7 to 8 cm, with no urethral meatus identified. There were testicular vessels on the left entering the left inguinal canal, associated with a hernia without internal content. No structure resembling a uterus was visualized. The right gonad was found near the right iliac vessels, and the respective vas deferens was not identified. A biopsy of the intra-abdominal right gonad revealed testicular hypoplasia.

For the evaluation and management of the case, a multidisciplinary meeting was held with the parents. Based on the observed findings and the parents' impressions, the consensus was to adjust the external genitalia to male anatomy. Since there was a possibility that the gonad located in the left labio-scrotal prominence could be functional and potentially able to promote spontaneous puberty, the decision was to preserve it, with regular and frequent follow-up due to the risk of gonadal malignancy.

DISCUSSION

Embryonic development of the reproductive system is a complex event that begins around the 7th week of gestation and requires a cascade of events involving the sequential and synchronized activation and suppression of various genes. For the differentiation of the indifferent gonad into a testis, the presence of the Y chromosome is essential, specifically the SRY gene. This gene triggers the production of the testis-determining factor, which leads to the formation of Leydig cells that produce testosterone, the male hormone. Testosterone, in turn, initiates the sequence of changes that results in the virilization of the external genitalia and, consequently, the development of a phenotype consistent with the male sex. Additionally, testosterone preserves the Wolffian duct and stimulates the migration of the gonads, differentiated into testes, to the labio-scrotal swellings. Through the peripheral conversion of testosterone into dihydrotestosterone (by the action of the enzyme 5-alpha-reductase), these swellings fuse and form the scrotal sac [4].

Another important hormone produced by the testis is the Müllerian inhibiting factor, which acts locally on the Müllerian ducts, preventing their development. If the SRY gene is not present, the gonads continue to develop as ovaries, leading the fetus to assume a female phenotype, with the preservation of the Müllerian ducts, which will later form the fallopian tubes, uterus, and the proximal portion of the vagina, along with the regression of the Wolffian ducts [4].

I see! Here's the translation of your text into English:

Sexual differentiation disorders (SDDs) consist of a group of alterations that occur at some point in this cascade of events, resulting in ambiguous phenotypes that can vary greatly and cannot be clearly classified as either female or male. This situation is referred to as ambiguous genitalia or genital ambiguity4. More objectively, some authors propose clinical parameters to consider its presence. For example, Lee et al.4 consider the diagnosis of ambiguous genitalia when the following criteria are present: 1) clear genital ambiguity; 2) when an apparently female genitalia presents with an enlarged clitoris and fusion of the labia majora; and 3) in the presence of genitalia that appears male with bilateral cryptorchidism, hypospadias, or micropenis.

The prenatal diagnosis of ambiguous genitalia, which affects approximately 1 in every 4,500 live births, presents challenges in various areas and has significant implications, including management of the pregnancy and planning for the baby's birth, as well as decisions regarding the sex of rearing and genetic counseling [5].

Currently, the assessment of genitalia through fetal ultrasound (FUS) is divided into two stages: early and later. The early assessment, conducted from 13 weeks of gestation, has an accuracy of nearly 100% and evaluates the angle between the ventral portion of the fetus and the axis of the genital tubercle. A male classification is given when this angle is greater than 30º, and a female classification is given when it is less than 10º. In the later stage of pregnancy, from 16 weeks onwards, direct visualization of the fetal genitalia is possible. In males, this is represented by a semicircular structure, the scrotum, with a penis in the midline; in contrast, a female genitalia appears as parallel echogenic lines representing the labia majora and minora[6]. Other findings to consider that assist in this identification include the presence of gonads within a structure compatible with a scrotum (indicative of testes), an enlarged phallus (suggestive of a penis), and the presence of a uterus, as well as the measurement of the rectovesical portion, also known as the anogenital distance6. However, factors such as maternal obesity, amniotic fluid volume, proximity of the umbilical cord to the genitalia, and an unfavorable fetal position for visualization can influence the accuracy of the examination.

The possibility of ambiguous genitalia should be considered whenever the sex of the fetus/infant cannot be determined through ultrasound evaluation [7]. Features such as a phallus with a rounded tip, abnormal curvature, and reduced size are suggestive of hypospadias [8]. Additionally, the observation of echogenic lines corresponding to the remnants of the prepuce, as well as the ventral deflection of the urinary stream (which can be visualized using color Doppler), support this diagnosis. The "tulip sign," which describes the appearance of a ventrally curved phallus between two labio-scrotal folds, is also noted [8].

Evaluation through three-dimensional ultrasound can also provide better visualization of genital structures due to its greater clarity and improved differentiation of structures. This also facilitates the visualization of the genitalia by parents and other members of the multidisciplinary team, helping in understanding the findings and development [9].

Additionally, fetal magnetic resonance imaging (MRI) can be used in prenatal diagnosis to provide detailed information about structures within the pelvis, such as internal genitalia, the urinary tract, or the rectum. It has the advantage of not being limited by maternal body composition, fetal position, or the presence of oligohydramnios. However, its main disadvantage is the long duration of the examination [6].

Thus, the identification of a potential genital abnormality in the fetus allows for its evaluation to begin during the prenatal period, through imaging tests, as previously discussed, as well as laboratory tests like fetal karyotyping. This test can be performed by obtaining material through invasive procedures such as amniocentesis and cordocentesis, and provides information about the fetal chromosomal composition, indicating whether it is typically female or male, or if there are any abnormalities [4].

After birth, various aspects need to be considered during the physical examination of the baby. These include the size and shape of the phallus, which helps in identifying conditions such as micropenis or clitoromegaly; the location of the urethral meatus, which may be found in different positions along the midline and ventral side of the penis, potentially indicating hypospadias; the presence of fusion of the labio-scrotal folds, which can suggest ambiguous genitalia; the location and size of the gonads, which may be small or absent, either in the abdomen, along the inguinal canal, or in the labio-scrotal fold; and the presence of inguinal masses, which may contain gonads or other structures, such as fallopian tubes or even a uterus [7].

In addition, laboratory tests are recommended to address any doubts regarding the function of the identified structures. These tests may include measurements of luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone, dihydrotestosterone, and androstenedione, depending on the clinical suspicion. It is important to note that, especially if the fetal karyotype has not been performed, it should be done, as its result is crucial for diagnosis. In particular cases, especially if there is uncertainty about the prenatal results or a need for confirmation, the importance of repeating the test should be evaluated [4].

Regarding the choice of gender for rearing, the birth certificate, which is currently issued shortly after birth, includes an option labeled "unknown" in the sex designation section. This allows for the newborn's registration to proceed even if the determination of the rearing gender takes additional time, considering the complexity of the cases. This option is also important due to the time typically required for a thorough evaluation [4].

Ambiguous genitalia is actually a finding that can be related to different etiologies. For instance, some authors categorize these causes into three groups based on the karyotype

results: the first, 46,XX (with congenital adrenal hyperplasia causing more than 90% of cases); the second, 46,XY (associated with various causes such as androgen insensitivity syndrome, pure gonadal dysgenesis XY, and 5-alpha-reductase deficiency); and finally, abnormalities of sex chromosomes, with or without the presence of mosaicism (such as Turner syndrome and DGM, which is associated with mosaicism 45,X/46,XY, as observed in our patient)[4].

The patient presented with a multicystic dysplastic kidney on the initial evaluation through ultrasound, which led to referral and further investigation at a specialized fetal medicine center. However, additional findings of abnormalities in the development of the external genitalia observed at this tertiary center, including what appeared to be hypospadias without associated urethral opening and seemingly fused and rugose labio-scrotal prominences, with the presence of a gonad on the left side, raised the suspicion of a disorder of sexual development (DSD). Therefore, it was recommended to perform fetal karyotyping during the prenatal period, which revealed the presence of mosaicism 45,X/46,XY.

In this case, the presence of ambiguous genitalia in the fetus, combined with the karyotype result showing mosaicism involving a sex chromosome alteration, categorizes the case into the third category of disorders of sexual development (DSD) previously described. Mosaicism 45,X/46,XY can present clinically in various ways and with different manifestations. Its spectrum can range from a seemingly normal man or one with infertility, a boy with short stature who may or may not have hypospadias and/or cryptorchidism, an individual with ambiguous genitalia, to a patient with Turner syndrome or a woman with secondary amenorrhea. However, it is only when mosaicism 45,X/46,XY is associated with ambiguous genitalia that it is classified as gonadal dysgenesis (GD). Within the spectrum related to this mosaicism, the presentation as MGD constitutes only a small fraction of cases, with the majority being individuals with a normal male presentation [1].

Some minor dysmorphic features or stigmata (including micrognathia, bilateral clinodactyly of the fifth fingers, and nail hypoplasia), as well as the renal abnormalities observed in our patient, can be explained by the 45,X lineage, as these findings are part of the clinical spectrum observed in Turner syndrome.

In discussing the issue of choosing the sex of rearing, a multidisciplinary meeting was held, considering the parents' perspective. It is crucial to emphasize the importance of collaborative work among specialists from different fields due to the complexity of the case and the need for informed and appropriate decisions in such situations. This search involves not only aesthetic considerations but also extremely relevant aspects concerning functionality. To seek more objective and concrete alternatives, various existing tools were utilized to further substantiate the decision made. Decisions regarding the baby's sex are only made after birth, as a more accurate and definitive assessment can only be conducted at that time. This consideration must include the expectations and understanding of the parents, who will provide their opinions on the case and, eventually, on the patient themselves. Three concepts must be considered in these cases: legal sex, where in this case, the patient has ambiguous genitalia but a decision was made to adapt it to male genitalia; sex of rearing, which refers to how the patient will be raised and treated by the parents; and gender, which refers to how the individual will perceive themselves in society, encompassing biopsychosocial aspects that may not necessarily align with the legal sex10. Therefore, the genitalia and the way it is reared do not define the patient's gender.

An example of this was the result observed using the Prader scale, a classification system initially created to assess the degree of virilization of the external genitalia in patients with congenital adrenal hyperplasia and a chromosomal constitution of 46,XX. The scale ranges from I to V. Upon examining the patient, it was noted that the characteristics, such as the size of the penis and the degree of labio-scrotal fusion with its roughness, were consistent with the level IV on this scale. This indicated a significant degree of virilization, which, as observed, was reflected in the parents' own perception of their child as a boy.

According to the masculinization score developed by Ahmed et al[2]. and applied by Cools et al.11, a patient with DGM, which considers findings related to external genitalia and ranges from 0 to 12, our patient had a score greater than 7. This was due to the fact that the patient had a phallus size within two standard deviations of the mean for their age, the presence of hypospadias, fusion of the labio-scrotal swellings (which were also rugose), and a palpable gonad in the scrotal sac with another visible in the abdominal cavity (both ovoid and with characteristics resembling those of a testicle). Additionally, the evaluation of internal sexual organs through laparoscopy did not reveal the presence of a uterus or fallopian tubes but did show testicular vessels on the left and a left vas deferens entering the inguinal canal on the same side. According to the management proposed by Cools et al.[11], it is recommended to perform orchiopexy of the gonad, with regular examinations of it, as well as annual ultrasound starting from puberty due to the possible risk of malignancy. A biopsy of the gonad should be performed before and after puberty to assess the risk of tumors, and in cases of precancerous changes or in situ neoplasia, the patient should undergo gonadectomy. The risk of malignancy of the gonad appears to be inversely related to the masculinization score of Ahmed et al.[2], meaning that a higher score (or greater virilization) is associated with a lower risk of neoplasia[11].

The gonad present alongside the labioscrotal prominence has the potential to be functional, and its preservation may allow the individual to produce hormones on their own, thus inducing and maintaining spontaneous puberty (i.e., without the need for medications to induce puberty)[11]. Therefore, in such cases, the risk (of gonadal malignancy) and the potential benefit (the development of spontaneous puberty) must be evaluated. It is important to highlight some points related to the choice of gender assignment, which we consider rel-

evant: 1) as mentioned previously, this choice involves not only aesthetic considerations but, more importantly, functional aspects, with the parents' impression being something that should be strongly taken into account; 2) the presence of a male lineage associated with mosaicism does not determine the choice of male gender assignment, as this option is complex and depends on other variables; 3) currently, some groups, based on the principle of autonomy, have proposed that the choice of gender assignment should be made by the individual with ambiguous genitalia when they are at an age where they possess the maturity and conditions to do so11, however, in our context, gender assignment is usually made primarily based on functional characteristics, expected surgical outcomes, and the family's perspective. Therefore, these decisions are not simple, and it is recommended that these cases be evaluated by multidisciplinary teams, particularly those experienced in such situations; 4) the choice of prophylactic orchiectomy should not influence the decision regarding gender assignment, as the choice to perform gonadectomy due to the risk of malignancy does not necessarily mean that the male option should be ruled out; and finally, 5) it is important to remember that there are different types of sex, such as anatomical sex, sex related to sexual activity, and gender identity, with the latter potentially differing from the one adopted. Nevertheless, as mentioned before, this decision is highly complex and challenging, weighing the benefits and potential risks, with the chosen option ultimately seeking to ensure the best well-being and quality of life for both the patient and their family[4,10,11].

CONCLUSION

Dealing with cases of ambiguous genitalia in the prenatal period presents great challenges for all parties involved, whether it be the family or the medical team, who must be aligned in the search for alternatives that prioritize the health of the individual, both physically and mentally. Multidisciplinary and collaborative work, aimed at finding the best alternatives, is therefore essential in these cases. Within this context, prenatal diagnosis is of significant importance, as it not only allows certain evaluations and tests to be carried out early on, but also facilitates the preparation of the family and the approaches to be adopted after birth. This complexity, due to the number and importance of the aspects to be considered in cases of genital ambiguity, makes them a real challenge for everyone who faces such a situation.

REFERENCES

1. Gantt PA, Byrd JR, Greenblatt RB, McDonough PG. A clinical and cytogenetic study of fifteen patients with 45,X/46XY gonadal dysgenesis. Fertil Steril. 1980 Sep;34(3):216-21.
2. Ahmed SF, Khwaja O, Hughes IA. The role of a clinical score in the assessment of ambiguous genitalia. BJU Int. 2000 Jan;85(1):120-4.
3. Prader A. Der genitalbefund beim pseudo-hermaphroditismus femininus des kongenitalen adrenogenitalen syndrome. Helv Paediat Acta 1954;9:231.
4. Stambough K, Magistrado L, Perez-Milicua G. Evaluation of ambiguous genitalia. Curr Opin Obstet Gynecol. 2019 Oct;31(5):303–8.
5. Lee PA, Houk CP, Ahmed SF, Hughes IA, LWPES Consensus Group; ESPE Consensus Group. Consensus Statement on Management of Intersex Disorders. Pediatrics. 2006 Aug 1;118(2):e488–500.
6. López Soto Á, Bueno González M, Urbano Reyes M, Carlos Moya Jiménez L, Beltrán Sánchez A, Garví Morcillo J, Velasco Martínez M, Luis Meseguer González J, Martínez Rivero I, García Izquierdo O. Imaging in fetal genital anomalies. Eur J Obstet Gynecol Reprod Biol. 2023 Apr;283:13–24.
7. Danish RK. Intersex problems in the neonate. Indian J Pediatr. 1982 Jul;49(4):555–75.
8. Meizner I. The 'tulip sign': a sonographic clue for in-utero diagnosis of severe hypospadias. Ultrasound Obstet Gynecol. 2002 Mar;19(3):317.
9. Cafici D, Iglesias A. Prenatal diagnosis of severe hypospadias with two- and three-dimensional sonography. J Ultrasound Med. 2002 Dec;21(12):1423–6.
10. Canella PRB. Sexo, sexualidade e gênero. Rev Bras Sex Humana [Internet]. 2020 Sep 19 [Cited 2024 Aug 27];17(1). Available from: https://sbrash.emnuvens.com.br/revista_sbrash/article/view/445. doi: 10.35919/rbsh.v17i1.445.
11. Cools M, Pleskacova J, Stoop H, Hoebeke P, Van Laecke E, Drop SL, Lebl J, Oosterhuis JW, Looijenga LH, Wolffenbuttel KP; Mosaicism Collaborative Group. Gonadal pathology and tumor risk in relation to clinical characteristics in patients with 45,X/46,XY mosaicism. J Clin Endocrinol Metab. 2011 Jul;96(7):E1171–80.

EDUARDO DE FREITAS KELSCH
http://lattes.cnpq.br/2843867645202852
https://orcid.org/0000-0002-2062-3307

MIRIAN FRANCINE FAVERO
https://lattes.cnpq.br/4898772654371090
https://orcid.org/0009-0003-8632-8225

THIAGO MENEZES CÉZAR
http://lattes.cnpq.br/9386847916618741
https://orcid.org/0000-0002-3817-5477

ISABELLA KAPCZINSKI MÜLLER
http://lattes.cnpq.br/6390175483712428
https://orcid.org/0000-0002-7267-4835

JORGE ALBERTO BIANCHI TELLES
http://lattes.cnpq.br/8253976877321806
https://orcid.org/0000-0002-8108-9638

RAFAEL FABIANO MACHADO ROSA
http://lattes.cnpq.br/7255679916272398
https://orcid.org/0000-0003-1317-642X

MAILING ADDRESS:
RAFAEL FABIANO MACHADO ROSA
Sarmento Leite, 245/403 - Porto Alegre - RS CEP:90.050-170
E-mail: rfmrosa@gmail.com

Scientific Editor - Heverton Pettersen
Spelling Check: Dario Alvares
Received: 10/10/23. Accepted: 05/09/24. Published: 24/09/24.
Updated: 02/12/24.