



Diagnostic and therapeutic approach in newborns with ambiguous genitale with disorder of sex development: consensus report of Turkish Neonatal and Pediatric Endocrinology and Diabetes Societies

Cinsiyet gelişim bozukluğu olan ambiguous genitelyalı yenidoğan bebeklerde tanı ve tedavi yaklaşımı: Türk Neonatoloji ve Çocuk Endokrinoloji ve Diyabet Dernekleri uzlaşısı raporu

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Abstract

Disorders of sex development are defined as conditions in which the chromosomal, gonadal, and anatomic sex is discordant. Patients usually present with atypical appearing genitalia. In the assessment of neonates with disorders of sex development, first, it is important to determine whether this situation requires prompt evaluation, and then the karyotype, hormone levels, and underlying etiology should be determined as soon as possible. All these procedures should be performed in the guidance of a multidisciplinary team in reference centers. As the physical examination of the infant is extremely important, the physician should suspect and then perform a detailed history and physical examination and lastly plan the required laboratory and imaging procedures for the definite diagnosis. It is important not to be hurried in the choice of sex. The aim of this article, which includes the diagnostic and therapeutic approaches in infants with ambiguous genitalia, was to provide a common practice for all pediatricians.

Keywords: Ambiguous genitalia, atypical genitalia, disorder of sex development, intersex, newborn

Öz

Cinsiyet gelişim bozuklukları kromozom yapısı, gonadlar ya da anatomik yapının birbiriyle uyumsuz olduğu durumlar olarak tanımlanır. Olgular genellikle kuşkulu atipik genitelya ile başvururlar. Cinsiyet gelişim bozuklukları şüphesi olan bir yenidoğanın ilk değerlendirilmesinde öncelikle yaşamı tehdit eden bir durumun olup olmadığı saptandıktan sonra, mümkün olan en hızlı şekilde karyotip, ilişkili hormon düzeyleri ve altta yatan etiyoloji belirlenmelidir. Tüm bu işlemler multi-disipliner bir ekip anlayışı ile referans merkezlerde gerçekleştirilmelidir. Burada bebeğin ilk muayenesi son derece önemli olup, hekimin öncelikle şüphelenmesi, sonrasında ayrıntılı öykü ve fizik bakı, laboratuvar ve görüntüleme ile tanıya yönelik planlamayı gerçekleştirmesi gerekmektedir. Cinsiyet seçiminde bu dönemde acele edilmemesi önemlidir. Atipik genitelyası olan bebeklerdeki tanı ve tedavi yaklaşımlarını içeren bu yazının amacı çocuk hekimlerinin bu konuda ortak bir yol izlemelerini sağlamaktır.

Anahtar sözcükler: Ambiguous genitelya, cinsiyet gelişim bozukluğu, intersex, kuşkulu genitelya, yenidoğan

Disorders of sex development (DSD) are defined as conditions in which the chromosomal, gonadal or anatomic structure are inconsistent arising from a defect in one of the sex development steps, especially in the first trimester. Different transcription factors, different signal molecules, and activation of different hormones are involved in the development of DSD. Therefore, assessment of a infant with DSD is difficult for pediatricians. Chromosomes, gonads, hormone synthesis, and efficiency of hormones should be evaluated systematically to determine which step is defective in addition to hormone production, and the status of the anatomic structures in babies with DSD. This whole process of assessment should be performed as promptly as possible and it is also very important to pay attention to the sensibility of families. In the initial assessment of a newborn with suspected DSD, it should primarily be determined if any life-threatening condition is present. Subsequently, investigations related with the karyotype, hormone levels, and underlying etiology should be completed as promptly as possible (1, 2). In this review, which was prepared by the Turkish Neonatal Society and Pediatric Endocrinology Society DSD Working Group, it was aimed to provide a mutual route for pediatricians in this area by establishing a common guideline including diagnostic and therapeutic approaches in babies with a suspicion of DSD.

Currently, DSDs are classified in three main groups including causes related with sex chromosome, 46, XY DSD and 46 XX DSD, with a definition system developed in the joint meeting held in Chicago in 2006 (Figure 1) (3, 4). DSDs, which are observed in 1 of approximately 4500-

5500 births, are characterized by at least 50 different congenital urogenital differentiation anomalies (3-5). DSD is a medical, social, and forensic emergency for affected patients in the neonatal period and infancy, because it involves many problems including sexual identity development disorder, hormonal disorders, and psychosocial differences, especially in the first two years of life.

The first examination of babies with DSD after delivery is very important because questions will be asked to physicians by families in relation with the baby's clinical status and sex. Although some cases of DSD can be identified easily immediately after delivery, the diagnosis may be delayed until childhood or adolescence in others. One should know that different external genitalia may be observed ranging from ambiguous genitalia to completely male appearance in individuals with 46,XX DSD and from ambiguous genitalia to completely female appearance in individuals with 46,XY DSD. Therefore, the first examination should be performed very carefully in the company of the family and the family should be informed.

Pediatricians should pay attention to the genital system evaluation during the first examination and have knowledge about the issue of when to be suspicious. In addition, pediatricians should know normal sexual development and genetic and hormonal conditions to explain this condition to the family. They should know that the gonadal tissue does not differentiate until the sixth gestational week and sex is basically determined by the presence or absence of male differentiation factors.

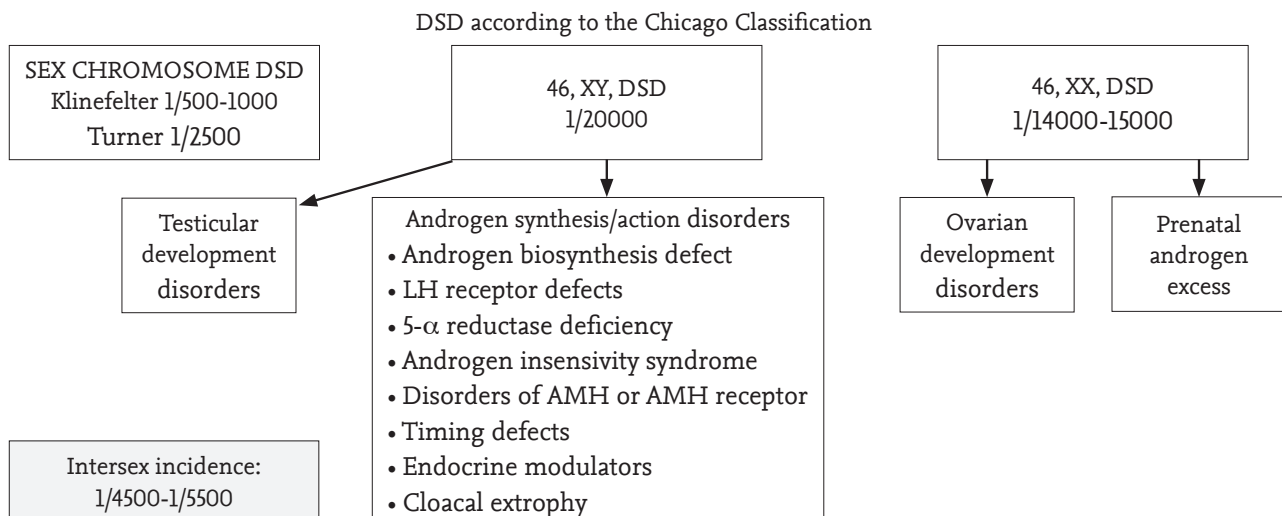


Figure 1. DSD according to the Chicago Classification

AMH: anti-mullerian hormone; DSD: disorder of sex development

Male sex differentiation is determined by the SRY gene located on the short arm of the Y chromosome. In the presence of the SRY gene, gonadal differentiation progresses in the direction of testicular formation and male genital structures develop with androgenic stimulation. At the same time, anti-Mullerian hormone (AMH) inhibits development of the fallopian tubes, uterus, and vagina. Virilization procedure in the external genital structures begins with transformation of testosterone to dihydrotestosterone (6). Physicians should know that any defect in the development of the genital structure will result in DSD and be should able to explain this to families.

Early diagnosis in these cases is important in terms of development of sex identity and because it has vital importance especially in terms of congenital adrenal hyperplasia (CAH). Therefore, early diagnostic and therapeutic approaches should be realized after a common assessment and decision process in a reference center, which involves certain divisions including mainly Pediatric Endocrinology, Child Psychiatry, Pediatric Urology or Pediatric Surgery, where all investigations and follow-up can be conducted. If possible, Medical Ethics, Forensic Medicine, Genetics, Pediatric Radiology, and a neonatologist, who monitors the patient, and a social service specialist should be included in this multidisciplinary approach. The decision procedure and informing should be completed by obtaining the family's views and opinions when necessary. It is very important to evaluate and direct each patient individually. In reference centers, the diagnosis can be made in a shorter time with a multidisciplinary approach and families are given standard information and enabled to feel more confident, while babies are given favorable care. In addition, families are allowed to learn previous experiences and the processes lived through by contact with previous families and to adopt the idea that this condition is being experienced by other parents and appropriate therapeutic approaches might exist. All branches involved in the diagnostic and therapeutic approach will contribute to education and case discussions related with DSD. It is thought that long-term follow-up results can be revealed with this approach (7).

1. Initial postpartum assessment and informing

Assessment of the genital system on the initial postpartum examination is important. Rapid and accurate sex designation by planning appropriate investigations for differential diagnosis in suspicious cases, referring the patient to a reference center to specify the etiology and long-term treatment plan, early diagnosis and treatment

of life-threatening metabolic conditions including CAH in risky cases, and assessment of long-term problems including sexual function and tumor development in the diagnostic process should be considered the most important target points. Here, the process of informing the family is very important; statements including "no sex" or "hermaphrodite" should be avoided, standard information should be given to families and contact with similar families should be targeted (8). Neonatologists and pediatricians are responsible for establishing coordination together with diagnostic assessment, accurate explanation of the medical condition to the family, stating that the final decision would be made after detailed assessment, and providing communication between the family and other physicians in the team (9, 10). This initial explanation is very important and it will be more difficult for the family to accept the situation if an erroneous statement is used. Initial explanation should be made in a positive, respectful, and optimistic manner, and a clear and open communication should be established with the family. At this time, the physician should inform the parents simultaneously, should not communicate with other family members without consent of the parents, and avoid any diagnosis or sex referral. At the initial contact meeting, the family should be told that they have a nice and healthy baby and terms such as "your baby" "your child" should be used. The initial examination should be performed in the presence of the family, if possible, and it should be explained that inadequate or excessive sex development disorder may be present in these babies, but they can live their lives with female or male sex (8). At this point, explanation of the sex development process with the help of diagrams and pictures in a simple and realistic way will help the family to understand the situation. During this meeting, the family should be clearly informed that they are not alone, this condition has not arisen from any mistake, they will always be told the truth and dealt with honestly, they will be included in the decision process, the child's future will also be considered in sex development and their baby's body would be respected throughout this whole process (11). It is very important to pay attention to the terminology used in communication with families, continuance of the informing process in a stepwise fashion, and have the Pediatric Endocrinology and Psychiatry Departments inform the family and record this informing in writing. The terminology currently recommended to be used in this setting is shown in Table 1 (12).

Most of babies with DSD are otherwise healthy and adrenal crisis is frequently not expected until the second

Table 1. Terminology recommended to be used in cases of ambiguous genitalia

Female child	Ambiguous Genitalia	Male child
Your daughter	Your baby	Your son
Clitoris	Phallus	Penis
Labia	Folds	Scrotum
Ovaries	Gonads	Testicle
Vagina, urethra	Urogenital sinus	Urethra

week in term babies. Therefore, these babies can be followed up in reference centers in ward rooms where they can stay with their mothers instead of neonatal intensive care units. This approach improves bonding between mothers and babies and reduces the trauma observed in some families (8).

2. The decision process

Being confronted with a baby with DSD and the diagnostic process involves stress and difficulties for both physicians and families. Although many factors including the etiology causing DSD, reproduction system anatomy, familial and cultural factors, and most importantly, long-term outcomes affect the decision process, the decision should be made individually in a case-based manner. The family's point of view is important together with surgical options, long-term hormone treatment and fertility potential, but it is not prioritized in the decision. In this process, the decision is made leisurely considering the child's benefit sometimes as a result of a follow-up period that would last for years in a reference center involving multiple disciplines including Pediatric Endocrinology, Pediatric Urology/ Pediatric Surgery, Child Psychiatry, and Radiology. The necessary urgent medical interventions should be initiated as soon as possible, but one should be patient in terms of surgical treatment and sex decision and not be hurried in the neonatal period. In particular, irreversible surgical decisions should be made very carefully. Generally, surgical operations are performed after the decision about sex and this process may be completed a very long time after the diagnosis. In some cases, it may be necessary to avoid surgical interventions until the child establishes his/her own gender identity. Conclusively, the decision of sex is not an emergency. This should be left to the gender selection commission who will monitor the patient for a long-term in terms of DSD. The decision of sex may be made in a very short time in the neonatal period in cases including congenital adrenal hyperplasia with the 46,XX karyotype and complete androgen insensitivity with the 46, XY karyotype, whereas for some

it may take years to make diagnoses. The etiology may be variable and each etiology is managed differently. Pediatric endocrinologists guide the sex determination commission and act as coordinators by contacting the family. Pediatric endocrinologists are involved in the diagnostic and therapeutic process throughout the long-term follow-up period, starting from the initial assessment process. Neonatologists are responsible for informing the family about the postnatal status of the baby and for coordination with the relevant disciplines. The child psychiatrist is the person who guides the process of gender identity development. An ethics specialist will help to solve clinical ethical problems during meetings. The objectives of this multidisciplinary team is to make the most accurate sex selection for the child, to give the necessary support to the family while providing integrated care, to continue education of the team consistently, to provide long-term follow-up of the patients, and to enable coordination of all teams. The decision should not be made considering only external genitalia examination or the opinion of a single person. The decision process should be completed with a consensus after a detailed investigation and assessment process according to the results of physical examination and laboratory tests also taking the family's opinion. After this process, treatment should be planned in an individualized, integrated, and evidence-based fashion according to the decisions of the gender determination commission. At this time period, families should be recommended to name their babies with names that can be used for both sexes (13, 14). It should be known that families are mostly sensitive about the following issues: the number of examinations should be kept as low as possible, examinations should be performed without harming the baby and after obtaining consent from the family. Conclusively, the initial interview and informing is very important and a similar speech can be made for families using the common statement shown in Attachment 1 in all centers. While informing the family, it should be emphasized that all options and potential problems will be considered.

3. Disorder of sex development suspicion

In the presence of ambiguous genitalia and in babies who have no determinate male or female external genitalia, one should be suspicious of a picture of DSD. Indeterminate male genital structure is frequently found in the presence of bilateral undescended testicles, severe hypospadias and/or bifid scrotum or in cases of undescended testicles accompanied by hypospadias. Clitoral hypertrophy, posterior labial fusion, and inguinal/labial

mass are the conditions that frequently raise suspicion in terms of female external genital structure (8). One should also be suspicious of DSD in the presence of micropenis (<2.5 cm) and in cases of discordant between genital appearance and karyotype.

Physicians who deal with this issue are responsible for determining life-threatening conditions in evaluation of babies with a suspicion of DSD, for timely diagnosis with differential diagnosis, and for giving reliable information to the family. The diagnostic process will be completed with the results obtained from appropriate laboratory tests and imaging methods following a detailed history and physical examination.

a. History taking

When a baby with ambiguous genitalia presents, family history of similar clinical picture and consanguinity between the mother and father should be interrogated. Maternal virilization, hormonal disorder, and drug (progesterone, steroid) use during pregnancy should also be interrogated. In addition, use of assistive reproduction technique and the results of the tests performed during the antenatal period (e.g., karyotype) should be questioned. In the family history, presence of unexplained death in the neonatal period or genital anomaly, water-salt loss, abnormal puberty development, amenorrhea or infertility should be investigated. Here, social history and perception of the event by the family should also be assessed (6).

b. Physical examination

Most cases of DSD including mainly ambiguous genitalia are diagnosed on the initial examination in the neonatal period. In suspected DSD cases, the baby should be examined after being completely undressed. On general physical examination, skin turgor, presence of low birth weight or intrauterine growth retardation, prematurity findings, developmental retardation and mid line defects, cloacal or anorectal anomalies and dysmorphic findings related with a probable syndrome should be evaluated. It should be kept in mind that small for gestational age (SGA) and other developmental anomalies may be found more frequently especially in individuals with XY DSD. Hyperpigmentation in the genital region or nipple region may be a warning for CAH. However, the serum 17-hydroxyprogesterone (7-OHP) level should be measured on the postnatal fourth day in cases with hyperpigmentation because normal familial variant may be present. Blood pressure should specifically be mea-

sured on physical examination. On examination of the genital system, the gonads, labioscrotal folds, phallus, and urogenital defects should be examined one by one. Labioscrotal folds or presence of gonads in the scrotum should be primarily evaluated. Subsequently, asymmetry, masculinization, and labioscrotal gonad status in the external genital structures, presence of swelling, pigmentation, fusion, and creases of the labioscrotal folds should be assessed with inspection and palpation. In addition, the presence of hernia should be investigated with palpation bilaterally in babies with female external genitalia. Although the gonads palpated are frequently testicles, it should be kept in mind that it may rarely be ovotesticle. Inguinal examination is very important in girls, even though normal phenotype is present. Diagnostic flow charts by presence of gonads and uterus are presented in Figures 2 and 3.

The mean testicular volume in a normal, term male baby is 1.1 mL. One should know that prepubic adipose tissue may lead to misinterpretation of the actual length. The phallus length measured by stretching from the penopubic junction to the head of the glans should be at least 2-3 cm and its width should be ≥ 0.9 cm in term babies. Reference stretched penile length measurements in both groups should be known because the penile length may show variance in term and preterm babies. The mean stretched penile length measurements in the neonatal period are shown in Table 2 (15).

Attention should be paid to hypospadias and the position of the urethral defect. There has been a marked increase in cases of hypospadias especially with the increasing frequency of use of assistive reproduction techniques. Presence or absence of chordae should be determined on physical examination in these babies. The inguinal canals should be evaluated in terms of gonads and the phallus length should be measured. It should be known that the testicles may not descend until the 34th week and the clitoris may appear larger because of small amount of adipose tissue in the labia in preterm babies. In addition, it should also be kept in mind that increased dehydroepiandrosterone sulphate (DHEA-S) levels may lead to cliteromegaly, and cliteromegaly frequently improves in the postnatal first month with decreasing DHEA-S in preterm babies. However, cliteromegaly in extremely preterm babies should be evaluated carefully because there are insufficient data related with normal clitoris size in extremely-low and very-low-birth-weight babies. In term babies, the normal clitoral width is 2-6 mm and

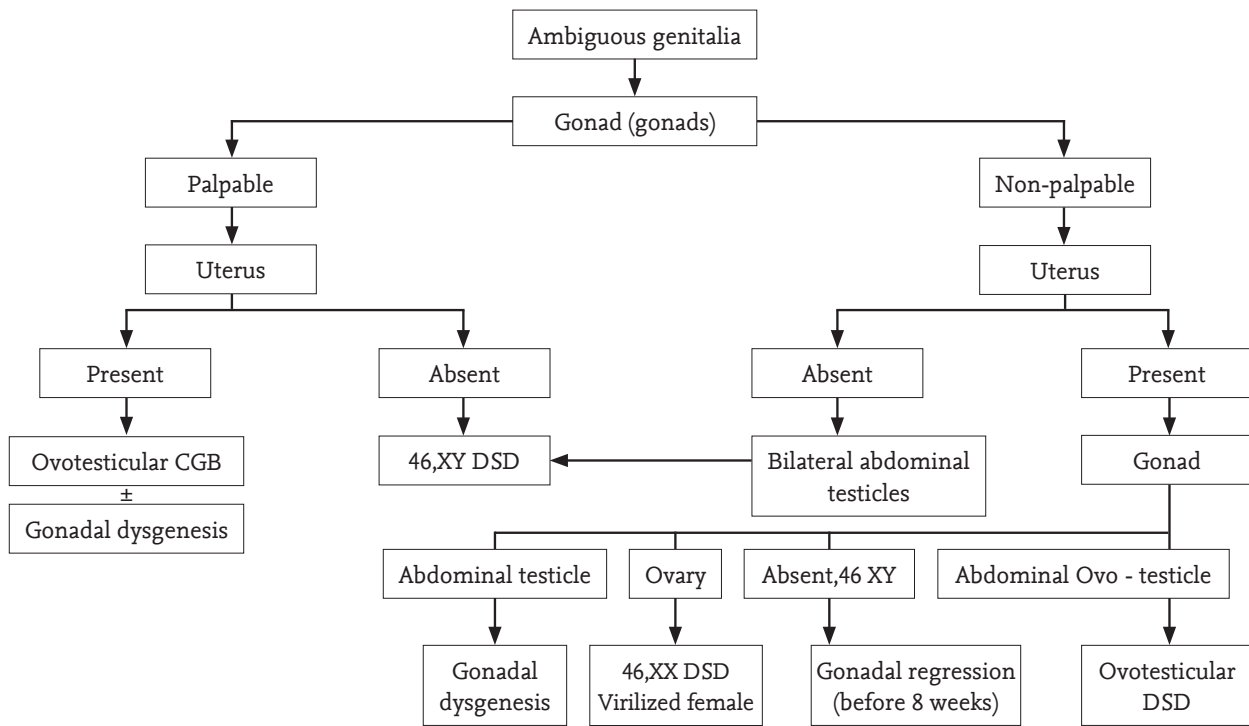


Figure 2. Approach by the status of gonads in cases of ambiguous genitalia [from the Pediatric Endocrinology and Diabetes Association Consensus in Pediatric Endocrinology Publications 2014(16)]

DSD: disorder of sex development

Table 2. Mean stretched penile length in term and preterm newborns

	Mean (cm)	Mean -2.5 SD
Term newborns	3.5±0.4	2.5
Preterm newborns (34 GW)	3.0±0.4	2.0
Preterm newborns (30 GW)	2.5±0.4	1.5

it should be considered abnormal if it is >9 mm. CAH should be definitely excluded in male babies with bilateral undescended testicles. Differential diagnosis in suspicious cases are shown in Figures 2 and 3 (16). External genitalia on physical examination should be evaluated according to the Prader staging system and external masculinization score (Figure 4) (8, 13, 17, 18).

c. Laboratory and imaging methods

Stepwise diagnostic assessment is recommended in cases suspicious of DSD. The diagnosis is frequently made according to clinical and morphologic assessment, endocrinologic investigations, and genetic studies. In the primary care setting, serum electrolytes should be studied together with serum 17-OHP, AMH, testosterone, androgen, cortisol, androstenedione, and gonadotropin levels, and urinalysis should be performed in terms of related renal anomalies. It should be kept

in mind that serum 17-OHP and androgen levels may not be reliable in the first 36-72 hours of life because of involution in the fetal zone, serum electrolyte levels may be normal in the first 4 days of life in the picture of salt-losing CAH, severe cases emerge frequently in the 2nd week and adrenal hormones in particular will give more accurate results after the 2nd day of life, and erroneous results in this physiologic transition period may lead to erroneous diagnosis. Therefore, hormonal tests will give reliable results if ordered at the appropriate time intervals. An increase in gonadotropins as an indication of mini puberty occurs after 1-2 weeks. The testosterone level is recommended to be measured in the postnatal 4-10th weeks as serum testosterone levels in male babies are low in the first 7-14 days of life and show a step-wise increase until the 2-3rd month (16). Internal genital organs and other accompanying potential anomalies should be evaluated with abdominal and especially pelvic ultrasonography, and further investigations including magnetic resonance imaging, genitogram, and laparoscopy should be considered, if necessary. Abnormal adrenal appearance on ultrasonography may be a marker for CAH. It should be known that an inability to see the uterus and/or ovaries on ultrasonography does not mean that these organs are absent. Ultrasonogra-

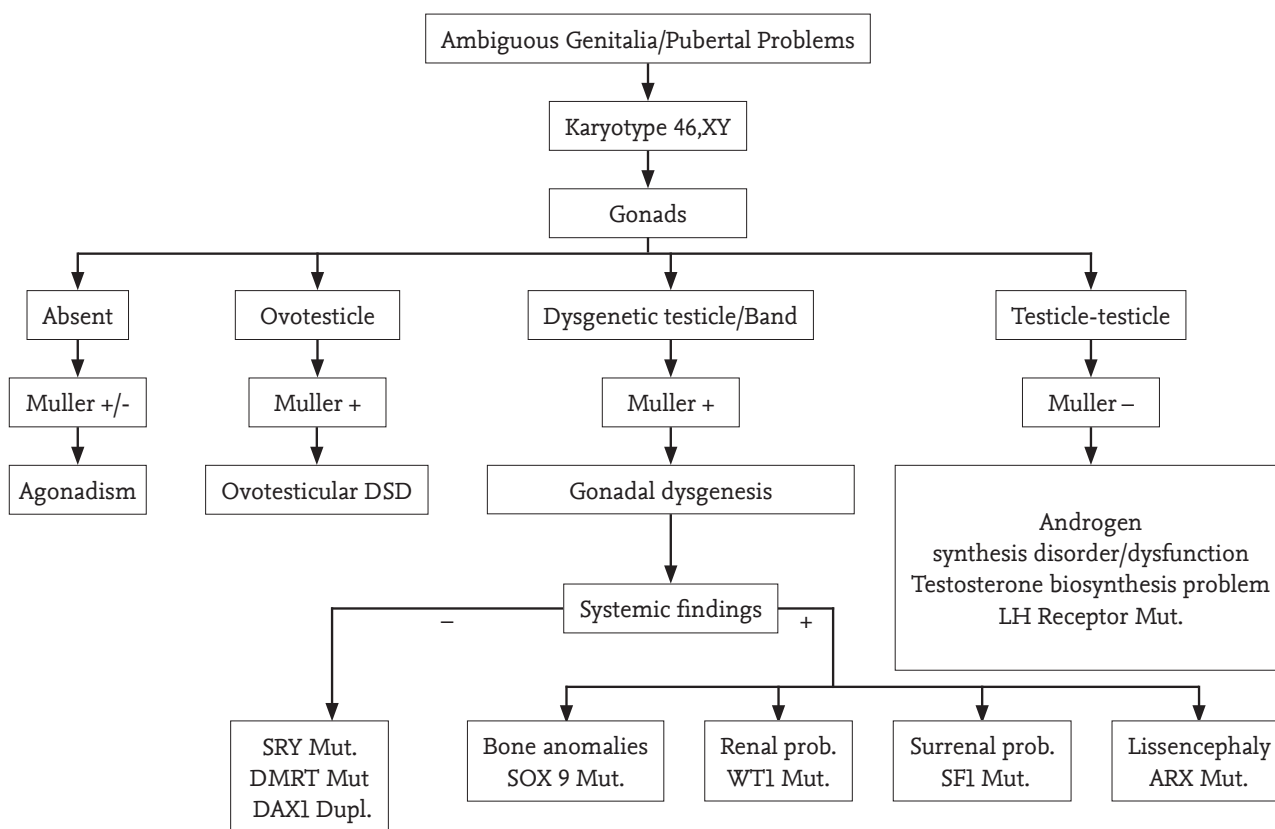


Figure 3. Approach by the status of gonads in cases ambiguous genitalia and pubertal problems [from the Pediatric Endocrinology and Diabetes Association Consensus in Pediatric Endocrinology Publications 2014(16)]

DSD: disorder of sex development

phy may give erroneous results if the baby is not well or the bladder is empty and its diagnostic success is related with experience. Although determination of karyotype is very important in the diagnostic approach, usually its result cannot be obtained in a time period shorter than 2 weeks. Therefore, sex chromosome analysis should be performed using methods that give rapid results in 24-48 hours with an accuracy near 100% and show presence of sex chromosomes or the SRY gene including fluorescence in situ hybridization (FISH), polymerase chain reaction (PCR) or quantitative fluorescent PCR (QFPCR), and subsequently a full karyotype analysis should follow this. The results of ultrasonography and karyotype analysis should be obtained in 48 hours, if possible. Methods that give rapid results should be primarily preferred with this objective. In recent years, it has been reported that combined interpretation of testosterone levels and serum AMH measurement would be more beneficial (Figure 5) (5, 8, 11, 13, 19, 20). After primary care investigations, secondary care assessments should be performed for the differential diagnosis and determination of underlying etiology. This is especially important for

preterm babies in whom obtaining blood samples is a problem. Adrenal investigations are ordered urgently from the fourth day in preterm babies in the practical approach because a large amount of blood should be obtained for all these tests. The other investigations can be ordered after the 15th day. Use of methods based on liquid chromatography/ mass spectroscopy (LC/MS) should be preferred for decreasing the amount of blood obtained and for the most accurate diagnosis. Primary and secondary care investigations are shown in Table 3.

Currently, developments in biochemical analytical methods enable measurement of steroid hormones and their metabolites both in the serum and urine with a high level of reliability and specificity. In addition, advances in molecular genetics and genomic technology shortens the diagnostic process further with use of novel, rapid, and reliable techniques (21). Therefore, use of these novel technologies in reference centers where the diagnostic and therapeutic process for babies with DSD will be conducted will provide great convenience for patients, families, and physicians.

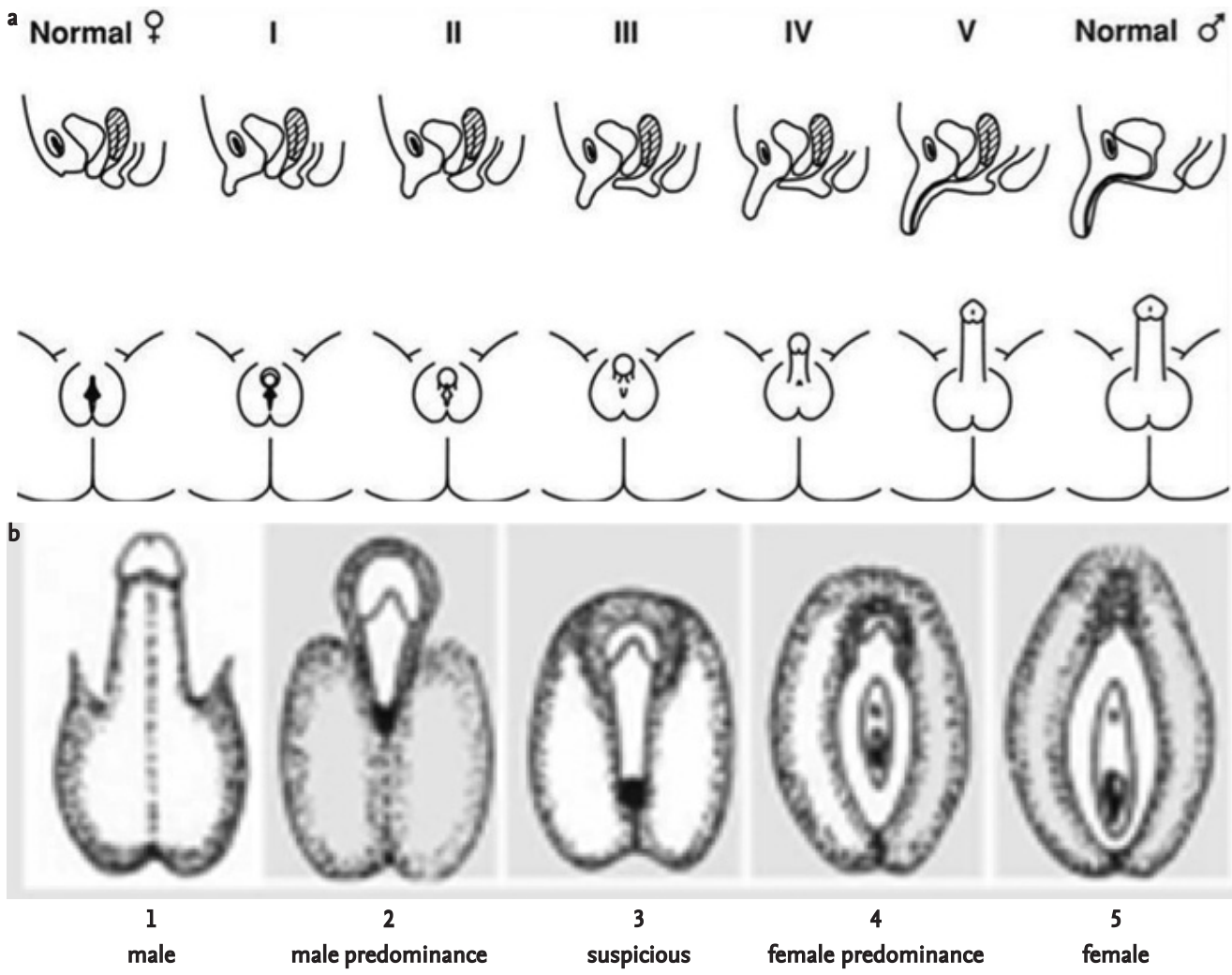


Figure 4. a,b. Prader (A) and Sinnecker (B) scoring systems

4. Congenital adrenal hyperplasia (CAH)

CAH is the most common DSD with autosomal recessive inheritance characterized by excessive production and accumulation of androgen and its compounds as a result of a defect in the steps of synthesis of cortisol from cholesterol in the adrenal cortex and frequently occurs in cases of 46, XX DSD. 21-hydroxylase deficiency is the most common form, which is observed in 90% of cases. It is especially observed in patients with bilateral non-palpable gonads and virilization. In these cases, in which Mullerian structures are observed on ultrasonography, 17-OHP is frequently increased. 21-hydroxylase deficiency, which is the classic form, is the most important cause of virilization. CAH occurs in three different types including simple virilizing (25%), salt-losing (75%), and delayed-onset CAH. The simple virilizing type is characterized by postnatal virilization and early pseudopuberty in girls with ambiguous genitalia and in boys with scrotal hyperpigmentation. The classic salt-losing form is char-

acterized by severe hyponatremic hyperkalemic dehydration, hypoglycemia, metabolic acidosis, hypovolemic shock, and mortality in cases with delayed diagnosis/treatment, frequently in the first week of life. Nutritional problems, vomiting, diarrhea, irritability, and lethargy are frequently present. The diagnosis is made with increased 17-OHP levels (>2000 ng/dL) in subjects with ambiguous genitalia, hyperpigmentation in the external genital organs, and signs of salt depletion on physical examination. It should be kept in mind that genital signs or any sign may not be present in male babies, but adrenal functions should be evaluated urgently in both sexes in suspicious cases. The risk of delayed diagnosis is high in patients with absence of scrotal hyperpigmentation. In treatment, hydrocortisone should be initiated at a dose of 20-25 mg/m² and mineralocorticoid including fludrocortisone should be added, if necessary. In cases of salt depletion, oral sodium supplementation may be needed and these patients should be urgently consulted with pe-

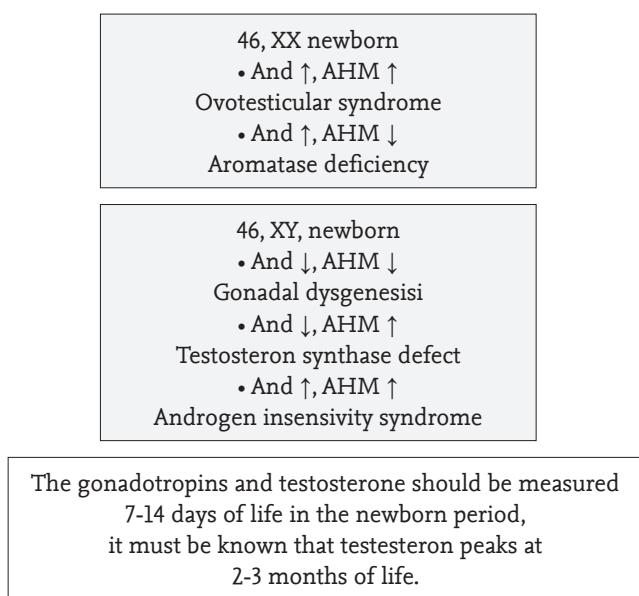


Figure 5. Differential diagnosis in cases of disorders of sex development according to androgen and anti-mullerian hormone measurement [Yau M, Khattab A, New MI. Prenatal diagnosis of congenital adrenal hyperplasia. *Endocrinol Metab Clin North Am* 2016 (20)].

AMH: anti-mullerian hormone; DSD: disorder of sex development

diatric endocrinology. Stress dose administration should be kept in mind in cases with febrile illness, surgery, trauma, and dehydration. In patients with CAH, hydration status, blood pressure, and blood glucose should be closely monitored in the neonatal period and families and healthcare personnel should be conscious of signs of jaundice, weight loss, and adrenal insufficiency, which may develop in these babies (6, 22).

Currently, cases of CAH can be diagnosed in the prenatal period. The objectives of this diagnosis include guiding families, initiation of steroid replacement to prevent adrenal crisis after delivery, and initiation of dexamethasone treatment when necessary. However, antenatal treatment is not administered routinely as it is considered to be experimental by many investigators (16, 20). The option of medical termination should not be presented to families in cases diagnosed prenatally, because life-threatening problems are not expected in the postnatal period.

a. Congenital adrenal hyperplasia screening programs in newborns

The objective of CAH screening, which was initiated in the United States in 1977 for the first time, and is currently

Table 3. Primary care and secondary care assessment in babies with suspicious disorder of sex development

Primary care assessment	Secondary care assessment
<ul style="list-style-type: none"> • Serum AMH • Serum 17-OH-progesterone • Testosterone, gonadotropins (LH, FSH) • Serum electrolytes • Urinalysis • Karyotype (FISH/PCR) • Abdominal/pelvic USG • Magnetic resonance imaging • Genitogram, laparoscopy 	<ul style="list-style-type: none"> • Serum human chorionic gonadotropin • Androstenedione, dihydrotestosterone, 11-deoxycortisol, DHEASO4 • Urinary steroid profile • ACTH stimulation test • Renin, aldosterone • DNA isolation for molecular genetics

ACTH: adrenocorticotropic hormone; AMH: anti-mullerian hormone; FISH: fluorescence in-situ hybridization; USG: ultrasonography; PCR: polymerase chain reaction

in effect in some other countries, is to prevent CAH-related morbidity and mortality, especially in male babies, by determining cases of salt-losing CAH. In addition, other objectives include to prevent the raising of female babies with severe virilization as boys and also to prevent psychosocial disorders related with excessive androgen production. The screening program is based on the measurement of 17-OHP on dried blood spots obtained on Guthrie paper. It is recommended that the blood sample should be obtained after the third day of life and studied using a fluorescence immunoassay or enzyme-linked immunosorbent assay. These levels should be evaluated by gestational week and birth weight as 17-OHP levels are increased in preterm babies. In addition, another blood sample should be sent 1-2 days later or second screening tests should be performed with high-performance liquid chromatography or liquid chromatography mass spectroscopy methods to increase accuracy. Although all these reasons limit routine use of CAH screening programs, the European and American Pediatric Endocrinology Associations recommend the use of CAH screening programs. In our country, it is thought that a CAH screening program might be included in the national screening program in the future according to the decision of the Pediatric Endocrinology Association and Ministry of Health on this issue.

In conclusion, the diagnosis of DSD is made as a result of using hormonal, genetic, molecular tests, and imaging methods following a detailed clinical assessment. Sex determination should be realized individually in a case-based fashion considering the sex identity developed in the baseline, diagnostic investigations and the family's sociocultural status with the common decision of a multidisciplinary team rather than according to a single physician's interpretation. In this time period, families should be informed appropriately and clearly and their concerns and thoughts should be respected. Physiologic sex should be specified as a result of investigations in all babies (23). With this objective, regional reference hospitals/centers should be specified to enable convenient, healthy, and reliable conduction of diagnostic and therapeutic processes in babies and children with DSD in our country. In addition, Gender Determination and Follow-up Committees composed of specialists including a pediatric endocrinologist, a child psychiatrist, a pediatric surgeon or pediatric urologist, a specialist of genetics, an adult endocrinologist, a deontologist, and a forensic medicine specialist should be established. These committees should fulfill their duties being responsible for the processes of examination, diagnosis and treatment, communication with families, sex determination, and specification of subsequent therapeutic options.

The actual objective of this article, which includes the definition, classification, diagnostic process, reference center characteristics, and therapeutic approaches in DSD is to provide an accurate approach for babies with ambiguous genitalia. In terms of diagnosis and sex selection, the definite diagnosis may be long-termed in cases of DSD and can be accomplished by certain centers. Another objective is to increase the number of reference centers where the most qualified and supportive approach will be presented to these babies and their families in the diagnostic and therapeutic process under the conditions of our country, and to increase access to these centers. It is thought that information obtained from these centers will be beneficial for patients, families, and physicians. In addition, establishment of associations and web-based organizations with the objective of enhancing adaptation and acceptance of families will be helpful. Communicating information to families about this disease by these ways and establishment of communication between families will decrease social problems related with this issue. With this article, it was aimed to reach the physicians working in institutions where patients with DSD frequently present initially. It is important to educate these physicians when

necessary in terms of standardizing the approach to these patients. Follow-up of subjects with DSD should be planned with a long-term perspective such that it will continue in childhood, adolescence, and adulthood.

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