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Plea for a standardized imaging approach to disorders of sex development in neonates: consensus proposal from European Society of Paediatric Radiology task force

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Abstract

This consensus article elaborated by the European Society for Paediatric Radiology task force on gastrointestinal and genitourinary imaging is intended to standardize the imaging approach in newborns with disorders of sex development. These newborns represent a difficult and stressful situation necessitating a multidisciplinary team approach. Imaging plays an important role in the work-up but needs to be optimized and customized to the patient. Ultrasound plays the central role in assessing the genital anatomy. The examination must be conducted in a detailed and systematic way. It must include transabdominal and transperineal approaches with adapted high-resolution transducers. The pelvic cavity, the genital folds, the inguinal areas and the adrenals must be evaluated as well as the rest of the abdominal cavity. A reporting template is proposed. The indications of magnetic resonance imaging and cysto- and genitography are discussed as well as they may provide additional information. Imaging findings must be reported cautiously using neutral wording as much as possible.

Keywords Adrenals · Congenital anomalies · Disorders of sex development · Genital tract · Magnetic resonance imaging · Neonates · Sexual differentiation · Ultrasound

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Introduction

Disorders of sex development (DSD) refers to a heterogeneous group of congenital conditions affecting human sex determination and differentiation. Its prevalence (including all types of DSD) is approximatively 1 in 300 births, or 1 in 5,000 births considering only significant genital ambiguities. It is a stressful, often unexpected, condition for the parents and the pediatrician. The birth of a child with DSD prompts a long-term management strategy involving numerous professionals working with the patient and family (ideally in a pediatric center with multidisciplinary expertise in this field). There has been significant progress in diagnosis, surgical techniques and psychosocial issues. Still, persisting controversial issues regarding classification, short and long work-up, treatment and ethical issues have led to several consensus statements. Imaging, especially pre- and postnatal ultrasound (US), plays a significant role in the diagnosis and the initial work-up of the neonate with DSD as it can easily provide information on the internal genital organs, the gonads, the adrenals and the rest of the abdominal cavity. Yet, imaging must be customized to the patient and standardized as much as possible. Furthermore, the results have to be integrated in the global work-up of the patient and the parents must be informed very carefully and cautiously. Wording is essential and the use of neutral terms must be the rule [1–6].

The aim of the present consensus paper is to propose standardized protocol for the US approach of neonates with DSD and to discuss the potential contribution of other imaging techniques based on a consensus among the members of the European Society for Paediatric Radiology (ESPR) abdominal task force and on the related literature (the manuscript was approved by the ESPR board on 14 Feb 2019).

Sexual differentiation

The components of physical sexual differentiation include chromosomes, gonads, and internal and external genitalia. The development occurs in two phases: *sex determination* and *sexual differentiation*. During the sex determination phase, around the 6th week, the undifferentiated gonad develops into testis or ovary. Sexual differentiation corresponds to the development of the phenotypic sex under the action of gonadal and other hormones.

In typical male development, actions of multiple genes including the SRY gene (on the Y chromosome) cause the development of testes. Primordial germ cells migrate to the gonad; furthermore, in early pregnancy, placental human chorionic gonadotropin stimulates the Leydig cells of the testes to produce androgens. Signaling through the androgen receptor then leads to the transformation of the Wolffian ducts into the internal genital structures such as vas deferens, seminal vesicles and epididymis. Anti-Müllerian hormone produced by the Sertoli cells of the testes induces the regression of the Müllerian ducts. Testosterone produced by the testes converts to dihydrotestosterone that leads to the fusion of the labio-scrotal folds, growth of the phallus and migration of the urethra to the tip of the penis. Most events occur in the first trimester. During the rest of the pregnancy, the penis will continue to grow and the testes will start their descent to the scrotum.

In typical female development, several genes located on the X chromosome and other autosomal genes (WNT4, R-Spondin 1 and FOXL2) prompt ovarian development. WNT4 gene is also required for the formation of the Müllerian structures (uterus, fallopian tubes, upper 1/3 of vagina). Lack of anti-Müllerian hormone allows the Müllerian structures to persist whereas lack of androgen leads to regression of the Wolffian ducts and development of the typical female external genitalia. Estrogen secretion is not required for the female developments [1, 4, 5].

Classification and nomenclature

The presently accepted classification of DSD is based on the sexual chromosomes: sex chromosome DSD, 46,XY DSD and 46,XX DSD (Table 1) [1].

Considerable progress has been made with understanding of the genetic basis of human sexual development, yet a specific molecular diagnosis is reached in only 20% of cases. The majority of virilized 46,XX neonates will have congenital adrenal hyperplasia, but only 50% of 46,XY children with DSD will receive a definitive diagnosis.

Clinical investigation

The approach to such patients must include detailed clinical examination, familial inquiry, and research into any particular finding or event that occurred during pregnancy (including obstetrical US findings). First-line testing includes karyotype with X- and Y-specific probe detection, genetic tests as available, measurements of 17-hydroxyprogesterone, testosterone, gonadotropins, AMH, serum electrolytes and urinalysis. US examination of the abdomen and pelvis is the primary imaging tool and is the basis for genital imaging in DSD [1–6].

Clinical examination

The clinical examination should include detailed analysis of the external genitalia: the gonads, labio-scrotal folds, phallus and urogenital openings. Findings in the male neonate

Table 1 Nomenclature for disorders of sex development (DSD; modified from [1])

1. Sex Chromosome DSD
  1.1 47,XXY (Klinefelter syndrome and variants)
  1.2 45,X (Turner syndrome and variants)
  1.3 45X/46,XY (mixed gonadal dysgenesis)
  1.4 46XX/46,XY (chimerism)
2. 46, XY DSD
  2.1 Disorders of gonadal (testicular) development
    2.1.1. Complete or partial gonadal dysgenesis (e.g., SRY, SF1, WT1)
    2.1.2. Ovotesticular DSD
  2.2. Disorders in androgen synthesis or action
    2.2.1. Disorders in synthesis
      2.2.1.1. Smith-Lemli-Opitz syndrome
      2.2.1.2. Luteinising hormone receptor mutation
      2.2.1.3. 5α-reductase 2
    2.2.2. Disorders in action
      2.2.2.1. Androgen insensivity syndrome
      2.2.2.2. Drugs and environmental factors
  2.3. Other
    2.3.1. Cloacal anomalies
    2.3.2. Robinow syndrome
    2.3.3. Persistant Müllerian duct syndrome
    2.3.4. Vanishing testis syndrome (testis regression)
3. 46, XX DSD
  3.1. Disorders of gonadal (ovarian) development
    3.1.1. Gonadal dysgenesis
    3.1.2. Ovotesticular DSD
    3.1.3. Testicular DSD (SRY+)
  3.2. Androgen excess
    3.2.1. Fetal
      3.2.1.1. 21-hydroxylase
      3.2.1.2. 11β-hydroxylase
    3.2.2. Fetoplacental
      3.2.2.1. Aromatase deficiency
    3.2.3. Maternal
      3.2.3.1. Maternal virilizing tumors
      3.2.3.2. Androgenic drugs
  3.3. Other
    3.3.1. Cloacal anomalies
    3.3.2. MURCS
    3.3.3. McKusick-Kaufman syndrome

MURCS Müllerian duct-aplasia-renal agenesis-cervicothoracic somite dysplasia association

favoring DSD include any phallic abnormality, undescended testes, bifid scrotum and hypospadias with undescended testes. In the female, fused labial folds, absence of normal perineal opening, clitoromegaly and any sign of virilization should raise such suspicion. In both sexes, findings suggestive of polymalformative syndromes may lead to the discovery of DSD (Table 2) [1–6].

Family history

Consanguineous marriages, previous familial cases of DSD or polymalformative syndromes with DSD (e.g., Smith-Lemli-Opitz syndrome) are potential tips. Previous cases of unexplained fetal death or prolonged infertility may be related to DSD.

Table 2 Syndromes and associations that may include disorders of sex development (DSD)

- Chromosomal anomalies
  Trisomies 13 and 18
  Triploidy
- Cornelia de Lange syndrome
- Fraser syndrome
- WT1 mutation
  Frasier syndrome
  Wilms tumor-aniridia (WAGR) syndrome
  Denys-Drash syndrome
- Fryns syndrome
- McKusick-Kaufman syndrome
- Noonan syndrome
- Robinow syndrome
- Russell–Silver syndrome
- Smith-Lemli-Opitz syndrome
- CHARGE syndrome
- Ectrodactyly ectodermal dysplasia syndrome
- Müllerian duct aplasia–renal agenesis–cervicothoracic somite dysplasia association (MURCS)

CHARGE coloboma, heart defects, choanal atresia, growth retardation, genital abnormalities and ear abnormalities

Course of the pregnancy

Phenotype/genotype discrepancy after chromosomal analysis and any other suggestive US finding (see below) are tips to the diagnosis. The use of some maternal medications may lead to a virilization or to undervirilization (progestin) of the fetus.

Imaging

Antenatal imaging

Fetal sex determination is important not only to satisfy parents but also to diagnose X-linked diseases, evaluating zygosity in twin pregnancies as well as evaluating DSD. The sagittal sign is the most common US sign to determine fetal sex during the first trimester. On a midline sagittal scan, a focal bulge can be visualized. The bulging is more vertical in a male fetus and horizontal in the female fetus. Based on this, the fetal sex can be determined accurately in 75% of cases around 13 weeks and 100% after 14 weeks.

Second-trimester sex determination is based on direct visualization of the penis and scrotum in male fetuses, labia majora and minora in female fetuses. The latter appear as four parallel lines. The overall accuracy of fetal sex determination in the second trimester ranges between 92% and 100%.

In addition to direct visualization of the external genitalia, other useful information for confirming fetal sex includes the presence and size of the fetal uterus in females, the fetal

scrotum and penis size as well as the testicular descent or fetal micturition in males.

The fetal uterus is best visualized in the fetal pelvis as a round mass behind the bladder corresponding to the enlarged cervix thanks to hormonal impregnation. It increases in size with advancing pregnancy as assessed by the transverse diameter (10 mm at 19 weeks to 20 mm at 38 mm). Penile length increases with advancing pregnancy from 6 mm at 16 weeks to 26 mm at 38 weeks. Testicular descent was observed in more than 85% of fetuses after 32 weeks; noteworthy, the testicular descent may be asymmetrical. Charts of testicular diameter during gestation have been published [7, 8].

Various findings leading suspicious for DSD:

In the male fetuses: micropenis, curved penis, hypospadias without testicular descent, peno-scrotal interposition. In the female fetuses: clitoromegaly (associated with or without adrenal hyperplasia), abnormal labial folds, absent uterus, inguinal hernia.

Phenotypic/genotypic discrepancy, suspected cloacal malformation and polymalformative syndromes are suspicious findings as well. Obtaining a detailed karyotype is mandatory in all cases. Any abnormality/finding has to be transmitted to the team that will take charge of the neonate with DSD [9, 10].

Neonatal ultrasound

US should be the first imaging method used to evaluate a neonate with DSD immediately after the clinical evaluation. Genito-cystography and magnetic resonance imaging (MRI) may have some specific contribution in selected cases.

Transabdominal and transperineal US using high-resolution curvilinear and linear transducers should be able to evaluate the normal internal genital organs in female fetuses. The neonatal uterus has a typical pear appearance with a large cervix and a thinner body (Fig. 1). The total height measures between 3 and 3.5 cm. The endometrial hyperechoic line can be visualized.

The gonads have typical appearances in normal neonates: Neonatal ovaries are usually large and contain follicles (due to materno-fetal impregnation) (Fig. 2), and testes have an oval shape and a central hyperechoic raphe (Fig. 3). Ovaries may be more difficult to localize due to masking intestinal air.

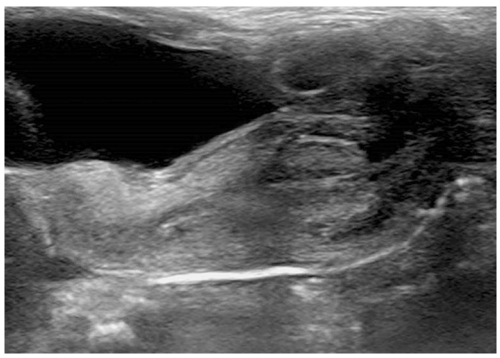

Fig. 1 A normal newborn girl. Sagittal sonogram shows the typical pear-shaped uterus with enlarged cervix compared with the body

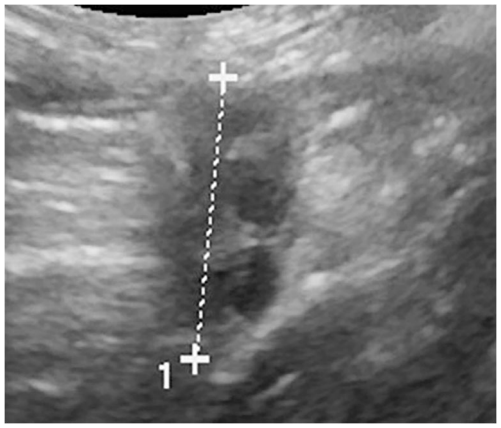

Fig. 2 A normal newborn girl. Ultrasound image of the left iliac fossa. The normal ovary (calipers) measures 2 cm between the crosses and displays multiple follicles

The rest of the abdominal cavity should be assessed to confirm the normal appearance (and size) of the adrenals, liver and bile ducts as well as the kidneys, bladder, pancreas and spleen. The adrenals have a typical appearance in the neonatal period (Fig. 4). They are hypertrophied due to a large fetal cortex and display a corticomedullary differentiation (hyperechoic medulla). They display a typical V or Y shape above the kidneys.

The brain should be examined as well whenever a polymalformative syndrome is suspected [11–15].

A pro forma for the customized and detailed US approach is suggested in Table 3.

In case of suspicion for DSD, the pelvis should be examined using both the transabdominal and perineal approaches. The examination should be systematic and detailed leaving any comments or conclusion at the end of the examination. One of the key features of the US examination would be to determine the presence or absence of a *uterus*. If present, it should be measured on a mid-sagittal plane (3–3.5 cm in a normal female newborn); the physiological pregnancy-related hormonal impregnation determines a pear-shape appearance (globular cervix) (Fig. 1). In the absence of hormonal

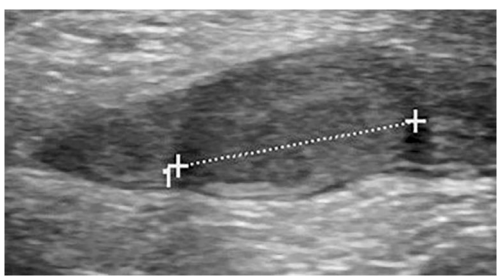

Fig. 3 A normal newborn boy. Ultrasound of the scrotum displays a normal oblong echogenic testis with a central echogenic linear raphe

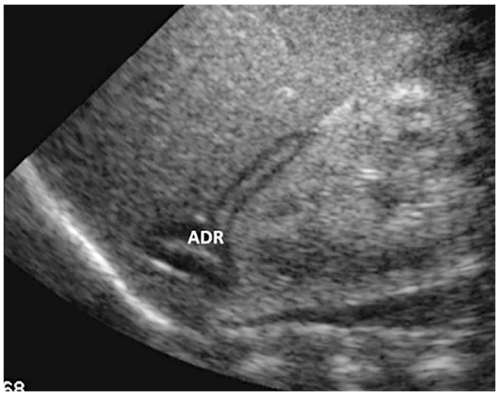

Fig. 4 A normal neonatal adrenal. Sagittal scan through the right kidney. The adrenal (*Adr*) displays a Y-shape with typical corticomedullary differentiation

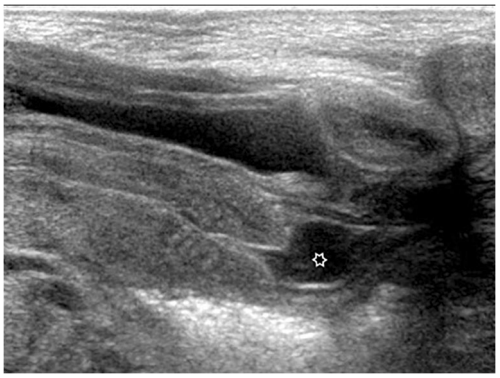

Fig. 5 The uterus without hormonal enlargement in a newborn with DSD. Sagittal scan of the uterus behind the bladder shows the uterus with a tubular shape as compared to Fig. 1. There is some fluid accumulation within the vagina (*star*)

enlargement, the uterus will have a rather tubular shape (Fig. 5). The next structure to verify is the presence or absence of a *vagina*. Whenever a uterus is visible, the vagina is present (at least the upper portion). Still, as the lower part of the vagina has a different embryological origin then the uterus, it may exist without a uterus (Fig. 6). Distention of the vagina may occur in cases of associated genital malformation, urogenital sinus (or cloacal anomaly) or virilization leading to a vagino-urethral fistula (Fig. 7). The transperineal approach is quite contributive to assess local anatomy (Fig. 6) especially when there is missing or supernumerary perineal openings.

The presence or absence of *gonads* should be checked. They may be present either in the expected location (Figs. 2 and 3) (iliac fossae for the ovaries, scrotum for the testes) or they may be ectopic, located higher in the abdominal cavity (and therefore more difficult to visualize), in the inguinal

Table 3 Proforma for ultrasound examinations in neonates with disorders of sex development

Transabdominal approach			
Uterus	Present/absent?		
	Hormonally enlarged?		
	Length:		
	Remarks:		
Vagina	Present/absent/distended?		
	Remarks:		
Gonads		Right	Left
	Present/absent?		
	Location (as expected/ abdominal/inguinal/labial):		
	Diameter:		
	Morphology (ovarian/testicular/undetermined):		
	Remarks:		
Adrenals	Size (normal/enlarged/enlarged cerebriform/small)"		
	Echogenicity (normal, absent corticomedullary differentiation/hyperechoic):		
	Remarks:		
Transperineal approach			
Number of perineal orifices			
Urethra	Identified?		
Vagina	Normal configuration (with uterus) or short (no uterus)?		
	Distended?		
Rectum	Identified?		
Abdominal ultrasound			
Urinary tract, liver and biliary tree, spleen, pancreas			

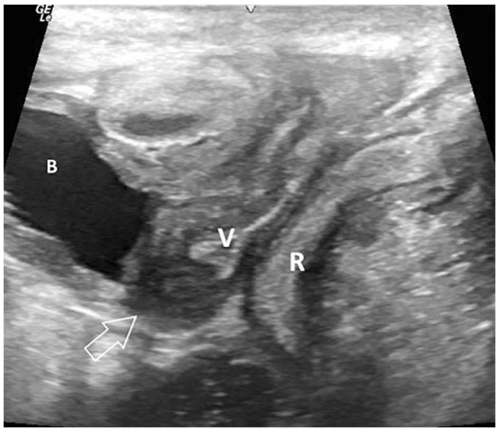

Fig. 6 Vagina without corresponding uterus in a newborn with DSD. Transperineal sagittal sonogram displays the vagina (*V*) with its fundus (*arrow*). The bladder (*B*) and the rectum (*R*) are normal

canals or within the labial folds (Fig. 7). The gonads should be measured (testes around 10 mm, ovaries around 15–20 mm). Their type should be defined: ovarian-type, testes-type or undetermined (Fig. (Figs. 2, 3, 8, 9). Both types of gonads may coexist [16–18].

Adrenal anomalies may be closely related to DSD especially, but not only, in cases of virilization of the neonate. The adrenals should be systematically analyzed. They appear normal in most cases (Fig. 4). Still, in cases of congenital adrenal hyperplasia they may appear globally enlarged or more typically enlarged with multiple folds, determining the ceribriform pattern (Fig. 10) (potentially already in utero). In congenital adrenal lipodystrophy, an extreme form of adrenogenital syndrome, they would appear more square-shaped and hyperechoic without the usual corticomedullary differentiation (Fig. 11). Furthermore, they will appear hypoplastic (<10 mm) in some polymalformative syndromes (Fig. 12) [15, 19–21].

As mentioned, the rest of the abdominal cavity must be examined to search for associated malformations .

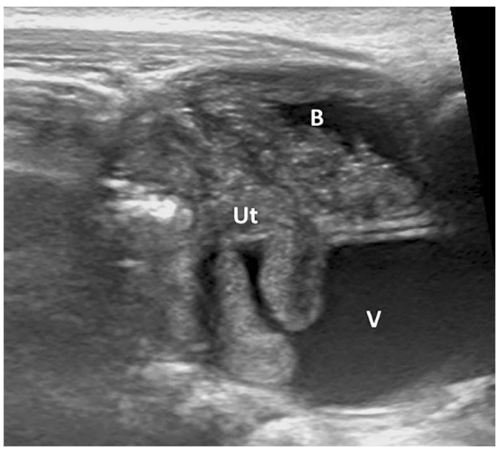

Fig. 7 A distended vagina (*V*) in a newborn girl with urethrovaginal fistula related to a congenital adrenal hyperplasia. Normal bladder (*B*) and uterus (*Ut*) are demonstrated

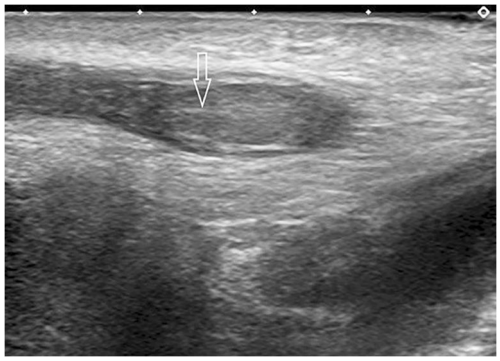

Fig. 8 Ectopic testis in the genital folds in a newborn with DSD. Sagittal scan of the left genital fold shows a testis-like gonad with a central raphe (*arrow*)

All informative data should be summarized and transmitted to the multidisciplinary team and to the parents, if possible in the presence of the pediatrician in charge of the patient, using neutral terms as much as possible (e.g. "Müllerian remnants" instead of uterus, "your baby" avoiding your son or daughter, etc.).

In a limited number of patients, such as those with congenital adrenal hyperplasia, the US findings are specific. This represents a minority of cases. In others, the US findings will have to be confirmed or completed by additional imaging examinations (see below).

Genito-cystography

Improvement of the US technique has significantly reduced the need for conventional vaginography to search for indirect evidence of the presence of a uterus. Still, some indications remain such as opacification of any supernumerary or reduced number of perineal orifices. Along with cystography, the technique would be used for the search for vagino-urethral fistula [16–18]. In some centers, depending on local experience and expertise, both techniques can be replaced by two-dimensional (2-D) and three-dimensional (3D) US. The US examination can be optimized after filling of the different

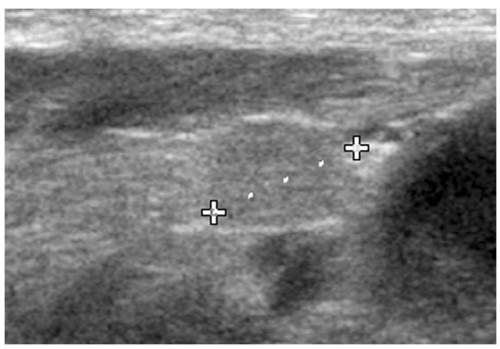

Fig. 9 An undetermined (neutral) type of gonad in a newborn with DSD. US of the left iliac fossa demonstrates a round nodule (calipers) without any features of a typical male or female gonad

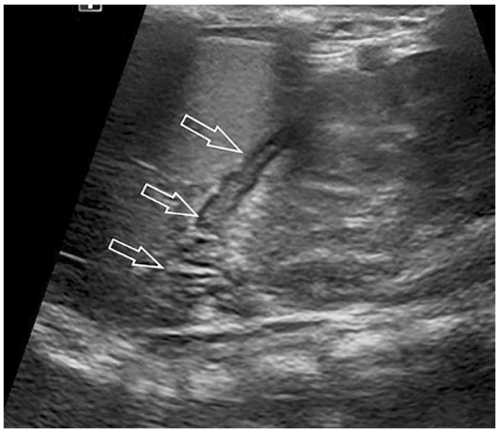

Fig. 10 The cerebriform pattern in a case of congenital adrenal hyperplasia in a newborn girl. Sagittal scan of the left adrenal displays a multilayered pattern (*arrows*)

perineal orifices with warmed saline fluid or with contrast-enhanced US [16–18, 22, 23].

Magnetic resonance imaging

Even in neonates, MRI may provide useful information in cases with complex genito-urinary malformations such as cloacal or uterovaginal anomalies as a complementary tool to US. Another interesting contribution could be to localize non-palpable gonads when US fails to localize them. MRI has a better sensitivity (86%) compared to US (76%) for detecting gonads [16–18, 24].

T2-weighted sequences provide the most pertinent information. The examination is performed without sedation; no contrast is injected. Protocols (and duration) of the examinations may vary depending on local equipment and experience.

Ectopic gonads, testes and non-cystic immature ovaries, have uniform high signal intensity at T2-weighted sequences. It's noteworthy that both type of gonads (testes and ovaries) may coexist in the same patient.

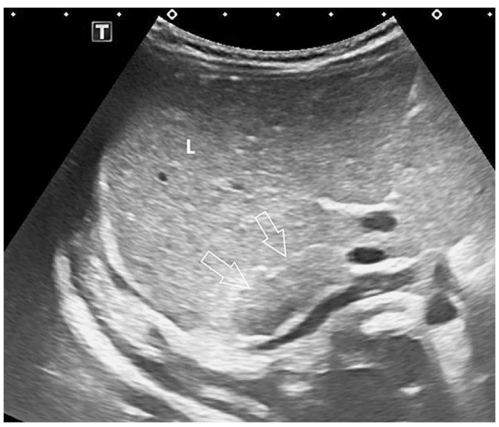

Fig. 11 Congenital adrenal lipodystrophy in a newborn with DSD. Transverse scan shows the right adrenal appearing square shaped, echogenic and without corticomedullary differentiation (*arrows*). *L* liver

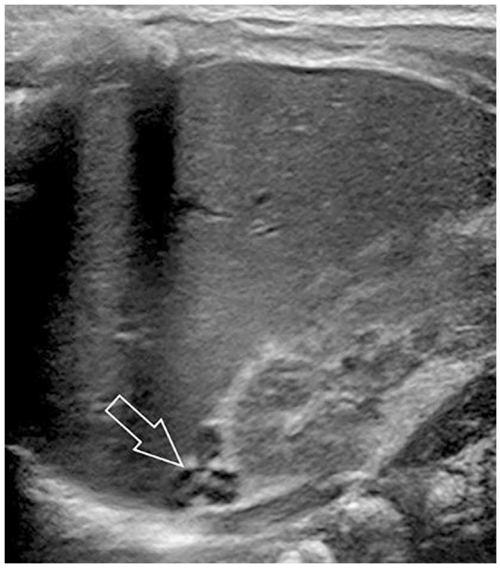

Fig. 12 Adrenal hypoplasia in a case of polymalformative syndrome in a newborn with DSD. Sagittal scan of the right kidney. The adrenal appears unusually short and small (*arrow*)

Conclusion

Radiologists involved in pre- and neonatal imaging of patients with DSD play an important role in diagnosis and treatment planning. US is the primary imaging modality. It should be optimized and customized to the patient following a detailed and standardized chart. The US examination should evaluate as precisely as possible the pelvic anatomy. MR imaging may provide additional information. Cysto- and/or vaginography should be performed when necessary. The results should be transmitted to the parents cautiously using appropriate terms in association with the pediatrician having in charge the patient.

Compliance with ethical standards

Conflicts of interest None

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