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Prenatal management of disorders of Sex development

Lyn S. Chitty [a,b,*], Pierre Chatelain [c], Katja P. Wolffenbuttel [d], Yves Aigrain [e]

[a] Clinical and Molecular Genetics Unit, UCL Institute of Child Health, 30 Guilford Street, London WC1N 1EH, UK
[b] Fetal Medicine Unit, University College London Hospitals NHS Foundation Trust, UK
[c] Service d'Endocinologie et Diabétologie Infantiles, Hopital Mère-Enfant de Lyon-Université Claude Bernard Lyon 1, Lyon, France
[d] Department of Pediatric Urology, Erasmus MC Sophia Children's Hospital, Room Sk 1272, P.O. Box 2060, 3000 CB Rotterdam, The Netherlands
[e] Université Paris Descartes, Hôpital Necker Enfants Malades, APHP Paris 149 rue de Sèvres, 75015 Paris, France

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Abstract Disorders of sex development (DSD) rarely present prenatally but, as they are very complex conditions, management should be directed by highly specialised medical teams to allow consideration of all aspects of diagnosis, treatment and ethical issues. In this brief review, we present an overview of the prenatal presentation and management of DSD, including the sonographic appearance of normal genitalia and methods of determining genetic sex, the prenatal management of pregnancies with the unexpected finding of genital ambiguity on prenatal ultrasound and a review of the prenatal management of pregnancies at high risk of DSD. As this is a rapidly developing field, management options will change over time, making the involvement of clinical geneticists, paediatric endocrinologists and urologists, as well as fetal medicine specialists, essential in the care of these complex pregnancies. The reader should also bear in mind that local social, ethical and legal aspects may also influence management.

Introduction

Disorders of sex development (DSD) are very challenging conditions requiring management by highly specialised medical teams to allow consideration of all aspects of diagnosis, treatment and ethical issues. Although rare, DSD is usually identified at the first physical examination after birth. However, in recent years, DSD has become more and more

* Corresponding author. Clinical and Molecular Genetics Unit, UCL Institute of Child Health, 30 Guilford Street, London WC1N 1EH, UK. Tel.: +44 0207 813 8533.
E-mail addresses: l.chitty@ucl.ac.uk (L.S. Chitty), pierre.chatelain@chu-lyon.fr (P. Chatelain), k.wolffenbuttel@erasmusmc.nl (K.P. Wolffenbuttel), yves.aigrain@nck.aphp.fr (Y. Aigrain).

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a prenatal medical issue. Probably the most common circumstance is a pregnancy presenting with a family history of an inherited form of DSD. Less common is the discovery of abnormal genitalia by prenatal ultrasonography or, and very rarely, discordance between the genetic sex determined by karyotyping, performed because of an increased risk of aneuploidy, and the phenotypic sex observed by ultrasonography. Ideally, these patients should be referred to a specialised multidisciplinary team including a pediatric endocrinologist, geneticist, paediatric radiologist and paediatric urological surgeon. This team should also have access to expertise in hormonal profiling and molecular genetics.

In this paper we shall briefly review some aspects regarding the prenatal presentation and management of DSD. We shall start by describing the sonographic appearance of normal genitalia and methods of determining genetic sex before discussing the prenatal management of pregnancies with the unexpected finding of genital ambiguity on prenatal ultrasound. Finally, we will review the prenatal management of pregnancies at high risk of DSD, keeping in mind that this is a rapidly developing field, dependent not only on the experience of the medical team but also patient access to advanced technical imaging and molecular genetic analyses. Local social, ethical and legal aspects may also influence management.

Normal appearances and evaluation of fetal genitalia

The appearance of normal fetal genitalia and the accuracy of sonographic fetal sex assignment across gestation are well documented [1,2]. However, reliable identification of fetal genital dysmorphology requires an experienced operator. In early pregnancy the genital tubercle is identical in size in male and female fetuses. From 12 weeks' gestation the critical observation is variation in the angle or 'sagittal sign' of the tubercle (Fig. 1) which allows for highly accurate sonographic identification of fetal sex using either 2-D (>95%) [3] or 3-D [4] ultrasound when performed by a skilled sonographer. The downward, or more obtuse angle, represents a female fetus and the upward, or acute angle, a male fetus. Sonographic assignment of fetal sex before 12 weeks' gestation is highly inaccurate [1,2].

Later in pregnancy, assignment is based on direct visualisation of the genital anatomy, including the scrotum and midline raphe of the penis in males, and the three lines, representing the labial lines, and uterus in female fetuses. There are charts of fetal penile length available but their utility has yet to be proven and different publications give slightly different normal ranges [5,6]. Three-dimensional ultrasound is of limited use for sonographic sex determination in routine practice, but it may be useful in defining malformations of the external genitalia. Colour flow Doppler ultrasound is not useful in defining normality, but it can be helpful in defining the extent of hypospadias if the origin of micturition can be identified (Fig. 2). Whilst there are descriptions of normal genital anatomy defined by in-utero magnetic resonance imaging [7,8], this modality is really of use in the evaluation of abnormal genitalia when it may add useful information regarding the genital anatomy, internal mullerian structures and other anatomical parts [9].

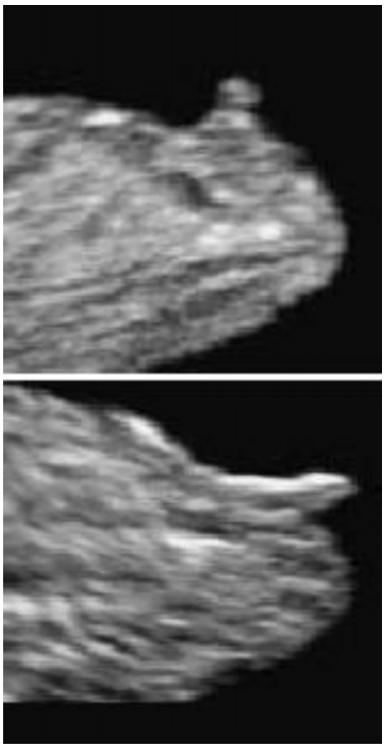

Figure 1 Showing the different angles of the phallus from 12 weeks gestation in a male (upper image) and female (lower image). Note the size of the phallus is equivalent in both, but it is the difference in angle that is diagnostic — acute in males and more obtuse in females.

Determination of genetic sex

Traditionally, determination of genetic sex has been performed by karyotype, fluorescent in-situ hybridisation

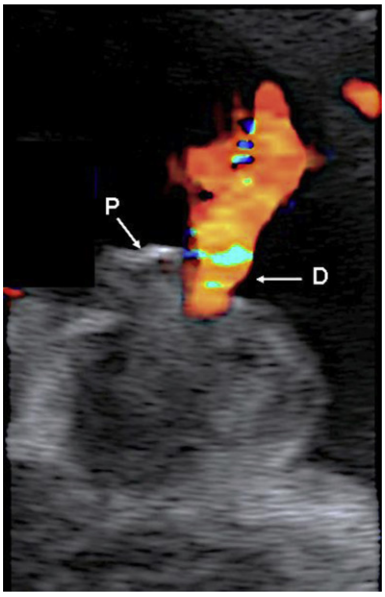

Figure 2 Doppler ultrasound showing urinary flow from a proximally placed urinary orifice (D) at the base of the short phallus (P). (Courtesy F Ushakov, London).