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Imaging and examination strategies of normal male and female sex development and anatomy

Lutz Wünsch*
Consultant Paediatric Surgeon and Urologist
Department of Paediatric Surgery, University of Lübeck, Ratzeburger Allee 160, 23538 Lübeck, Germany

Justine M. Schober
Consultant Paediatric Urologist
Pediatric Urology, Hamot Medical Centre, PA Eire, USA

Over recent years a variety of new details on the developmental biology of sexual differentiation has been discovered. Moreover, important advances have been made in imaging and examination strategies for urogenital organs, and these have added new knowledge to our understanding of the 'normal' anatomy of the sexes. Both aspects contribute to the comprehension of phenotypic sex development, but they are not commonly presented in the same context. This will be attempted in this chapter, which aims to link discoveries in developmental biology to anatomical details shown by modern examination techniques. A review of the literature concerning the link between sexual development and imaging of urogenital organs was performed. Genes, proteins and pathways related to sexual differentiation were related to some organotypic features revealed by clinical examination techniques. Early 'organotypic' patterns can be identified in prostatic, urethral and genital development and followed into postnatal life. New imaging and endoscopy techniques allow for detailed descriptive anatomical studies, hopefully resulting in a broader understanding of sex development and a better genotype–phenotype correlation in defined disorders. Clinical description relying on imaging techniques should be related to knowledge of the genetic and endocrine factors influencing sex development in a specific and stepwise manner.

Key words: gonadal development; imaging of testis; imaging of genital organs; fallopian tube.

Much progress has been made in both imaging of urogenital organs and understanding of developmental biology related to sex development and its disorders. Also, sex

* Corresponding author. Tel.: +49 451 5002581; Fax: +49 451 5006206.
E-mail address: wuensch@medinf.mu-luebeck.de (L. Wünsch).

development is becoming increasingly understood at the molecular level, and many phenotypic changes can be related to the expression of specific genes, proteins and pathways. Normal anatomy is the result, but the concept of a normal phenotype is not limited to external appearance. Modern imaging techniques and endoscopy show anatomical structures in unprecedented detail. However, for the interpretation of new discoveries, specialists from different disciplines depend on each other. Developmental biologists often work with animal models to study genotype–phenotype associations. They may be unaware that now very discrete anatomical details can be visualized in humans, making them available for detailed studies. Clinicians using imaging and endoscopy are excited by the quality of the images they obtain, but the interpretation of new findings relies on knowledge of normal anatomy and its developmental context.

Considering that disorders of sexual development (DSD) are among the most common birth defects[1], a reference range of normal sex development is essential to define whether and when a variation or disorder is present. The range of normality is also relevant if surgery is considered to attempt to normalize appearance, or when the results of surgery are evaluated.[2,3]

This review aims to combine basic aspects of sexual development with observable features with clinical relevance. Its purpose is to provide a link between progress in developmental biology and morphological features that can be evaluated by modern imaging technology or endoscopy.

Sex development has been extensively studied because of the visible phenotypic changes following genetic sex determination. As a consequence of its bipotential nature, the gonad is a particularly interesting model system in which to study organogenesis.[3] There are several excellent recent reviews on sex development.[1,4–7]

Sex development can be divided into three phases. In the first phase the chromosomal sex is established at fertilization. Male sex determination occurs under the control of a functioning SRY gene. Because, rarely, SRY-negative males have been described, a role for a 'suppressor of a male development suppressor' has been hypothesized.[1]

In contrast, it has long been held that ovarian formation is passive and constitutes an event that happens in the absence of testicular formation but requires two functional X chromosomes. It is possible, however, that there is a counterpart to testis-determining factor in females that determines ovarian differentiation (see Chapter 3). Deletions from Xp or Xq or both have indicated that genes from both arms of the X chromosome are involved in ovarian differentiation and maturation.[7–9] On Xq in the paracentromeric region there is a location for androgen receptor protein and for X inactivation. In female mammals this is important for dosage inactivation of one X chromosome.[10] Random inactivation is fixed for each cell and its progeny, so that each female is a mosaic of paternal and maternal active X chromosomes.

The second phase is the structural differentiation of the gonads. Development of the reproductive tract begins in the embryo and is sex-independent. In the human the embryonic period spans weeks 2–8 of gestation.[11] Until the fetus reaches 50 mm CR length (9 weeks) the genitalia in both sexes look identical.[12] Germ cells appear in the epiblast and migrate through the primitive streak, and then to the base of the allantois. Along the wall of the hindgut they migrate to the urogenital ridge.[6] In the primitive gonad, primitive sex cords displaying a corticomedullary architecture are formed by the end of the 6th week.[13]

The third phase is the development of the phenotypic sex, comprising internal and external genitalia, due to hormone-mediated differentiation processes.

Genes, proteins, and the respective pathways are summarized in Table 1.