Approach to the Infant with a Suspected Disorder of Sex Development

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KEYWORDS

• Disorders of sex development • Genital ambiguity • Sexual differentiation
• Congenital adrenal hyperplasia • Androgen insensitivity syndrome • Family support
• Gender assignment

KEY POINTS

- A thoughtful approach to the diagnostic evaluation of infants with a suspected disorder of sex development can optimize the process of reaching a diagnosis and assigning a gender.
- Psychosocial support to families is a critical aspect of comprehensive care.
- Referral to a multidisciplinary team with expertise in the care of disorders of sex development is recommended.

INTRODUCTION

A request to see a newborn with genital ambiguity is an uncommon experience in the career of most pediatricians. However, when including the full range of disorders of sex development (DSD), the prevalence is approximately 1 in 1500 births with significant genital ambiguity found in about 1 in 5000 births.[1] The pediatrician is faced with the clinical concerns of acute threats to the infant's clinical status, establishing a differential diagnosis, determining appropriate investigations and, importantly, providing explanation and support to the parents in an honest and sensitive way. This article reviews normal sexual differentiation, highlights key points in the medical history and physical examination noting normal findings, suggests a rational approach to investigation, and provides guidance on support for parents and families.

SEXUAL DIFFERENTIATION

The components of physical sexual differentiation include chromosomes, gonads, and internal and external genitalia. Other important concepts include gender identity,

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one's internal sense of gender, and gender role, one's gender-related behavior and interests in society. The recognition that all infants begin sexual differentiation with the same bipotential structures and that the expression of many genes, transcription factors, enzymes, and receptors leads to typical male and female development is critical (Fig. 1). Explanation of these concepts to parents is helpful in describing how atypical sexual differentiation occurs.

Development occurs in 2 phases, first "sex determination", the development of the undifferentiated gonad into a testis or ovary and then, "sexual differentiation", where phenotypic sex develops through the action of gonadal and other hormones. In typical male development, action of the SRY gene (which resides on the Y chromosome) and many other genes lead to the development of testes at around 6 weeks of gestation. Primordial germ cells then migrate to the gonad. In early pregnancy human chorionic gonadotropin (hCG) stimulates the Leydig cells of the testes to produce androgens. Luteinizing hormone (LH) from the pituitary gland takes over this function during the second and third trimesters. Signaling through the androgen receptor then leads to the development of the Wolffian ducts to form the internal genital structures of vas deferens, seminal vesicles, and epididymis during the first trimester. Anti-Müllerian hormone (AMH) production by the Sertoli cells of the testes leads to regression of the Müllerian ducts. Androgens and AMH act on the internal genitalia in a local fashion. Testosterone converted in the external genital structures to dihydrotestosterone (DHT) by the enzyme, 5α-reductase, leads to pigmentation, rugation, and fusion of the labioscrotal folds, growth of the phallic structure to form the penis, and migration of the urethra to the tip of the penis. The majority of these events occur in the first

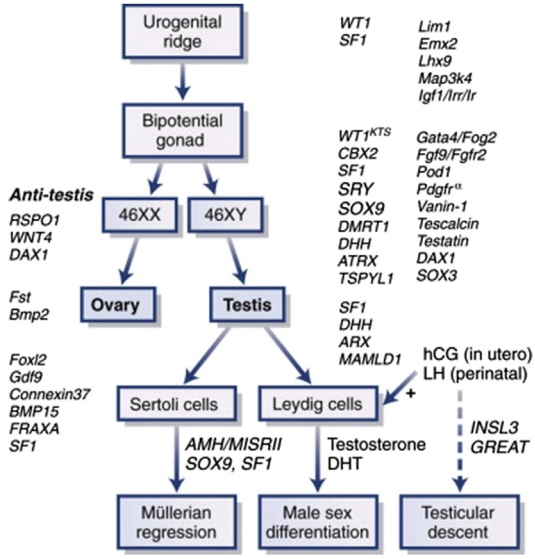

Fig. 1. Overview of the major events involved in sex determination and sex differentiation. Mutations or deletions in the genes shown in upper case letters have been reported or proposed as causes of disorders of sex development or gonadal failure in humans. The genes and factors shown in lower case letters have been proposed to play an important role in sex development, largely from studies of mice. DHT, dihydrotestosterone; hCG, human chorionic gonadotropin; LH, luteinizing hormone. (*From* Kronenberg HM, Melmed S, Polonsky KS, et al. Textbook of Endocrinology, 12th edition. Philadelphia: Elsevier; 2011. p. 868–934; with permission.)