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Intersex Conditions

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Intersex Conditions

J. Christopher Austin, MD

INTRODUCTION

Ambiguous genitalia and intersex are rarely encountered conditions. Whereas normally, the birth of a baby is heralded by the announcement of the sex just after delivery, in some cases the genitalia are abnormally developed, making determination of the baby's sex uncertain. When these rare circumstances occur, the situation can be extremely stressful and tense for the family and the evaluating team. An urgent, timely, and complete evaluation is mandatory. Hasty decisions or predictions should be avoided. Given the tremendous burden of assigning gender, a multidisciplinary team approach is crucial and should include a pediatric urologist, endocrinologist, and neonatologist. In this review, the more common intersex conditions are discussed, including those that present without ambiguous genitalia.

NORMAL EMBRYOLOGIC DEVELOPMENT OF THE REPRODUCTIVE SYSTEM

Sexual development begins with the formation of a bipotential gonad (**Figure 1**). Although several genes appear to play a role in this process, one of the more important genes clinically is the Wilms' tumor suppression gene (*WT1*).¹ *WT1* is expressed early during development of the genitourinary tract, and defects in *WT1* can cause intersex conditions (eg, Denys-Drash syndrome).² Differentiation to a testis versus an ovary is dependent on genes that are found on the sex chromosomes. The Y chromosome expresses testis-determining genes, most notably *SRY* (sex-determining region Y-chromosome).^{3,4} This begins the process of differentiation from the bipotential gonad into a testis. In the absence of the expression of testis-determining genes, the gonad differentiates into an ovary. The testis contains Sertoli cells and Leydig cells. The Sertoli cells produce müllerian inhibiting substance (MIS), which causes local regression of the ipsilateral müllerian (mesonephric) ducts, leaving only small, vestigial, remnants—the testicular appendages and the prostatic utricle.⁵⁻⁷ Leydig cells produce testosterone, which acts

locally to stimulate development of the ipsilateral wolffian (paramesonephric) ducts, forming the seminal vesicle, vas deferens, and epididymis. Through the conversion of testosterone to dihydrotestosterone (DHT), the genital tubercle and labioscrotal folds develop into male external genitalia.^{8,9}

Gonadal development in the female was classically thought to follow a “default” or automatic pathway, which could only be altered by the expression of testis-determining factor. This is probably not completely correct, as there now is evidence in animal studies that ovarian-specific genes are expressed and necessary for ovarian development.¹⁰ The lack of MIS production allows the müllerian ducts to develop into the uterus, fallopian tube, and proximal vagina. In the absence of testosterone stimulation, the wolffian ducts regress and female external genitalia form.

Intersex is a difficult and confusing subject. If approached systematically with a basic understanding of the embryology of gonadal and genital development, however, it is much more manageable. There are 2 basic categories of intersex disorders—those that are caused by improper development of the gonads, and those that are the result of aberrant (a deficiency or excess of) activity of the hormones produced by the gonads.

CONGENITAL ADRENAL HYPERPLASIA

CASE 1 PRESENTATION

An 8-day-old baby is hospitalized for failure to thrive. The child was noted to have what appeared to be hypospadias and bilaterally undescended, nonpalpable testes. The parents were told their baby was a boy, and the child was discharged on day of life 2. At admission, the child was hypotensive. Results of serum blood chemistries are notable for hyponatremia and hyperkalemia.

- **What is the differential diagnosis and appropriate evaluation for this infant?**