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Pragmatic approach to intersex, including genital ambiguity, in the newborn

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ABSTRACT

The evaluation and management of a newborn with ambiguous genitalia must be undertaken as quickly as possible and with great sensitivity for the child's family. Where possible, a comprehensive team approach with a pediatric urologist, endocrinologist, geneticist, neonatologist, and child psychiatrist/psychologist should work closely with the family to establish the diagnosis and determine gender. Although the preferred gender assignment is not always clear, a thorough examination of endocrine function, karyotype, and potential for fertility should guide the determination. While some disorders of sex development (DSD) sex assignments are relatively straightforward, those with more advanced genital ambiguity and unclear gonadal function represent a major challenge. A child's phenotypic sex results from the differentiation of internal ducts and external genitalia under the influence of hormones and transcription factors. Any discordance among these processes results in ambiguous genitalia or DSD. Currently, the main categories of DSD are 46,XX DSD, 46,XY DSD, sex chromosome DSD, ovotesticular DSD, and 46,XX testicular DSD. Priority is given to rule out more immediate life-threatening disorders like salt wasting CAH. Many centers in the United States lack the comprehensive "team members" and not all conditions necessitate this team approach. This article aims to provide guidance for initial workup and identify the specific conditions for which expert guidance is needed.

Introduction

For an infant born with ambiguous genitalia, initial assessment should be directed to determine if there is a life-threatening situation and then evaluate as quickly as possible the karyotype, indicated hormonal profiles and, as far as possible the underlying etiology. While it has been generally agreed that optimal care for infants with disorders of sex development (DSD) involves an experienced multidisciplinary team,[1] there are very few centers that have such teams and there is as yet no verification process for a designation as "centers of excellence." Since it is recognized that many health care facilities are resource poor in this regard and do not have the requisite experts to form such a complete team, there is a need for information regarding what type of evaluation of the newborn with DSD should be done initially

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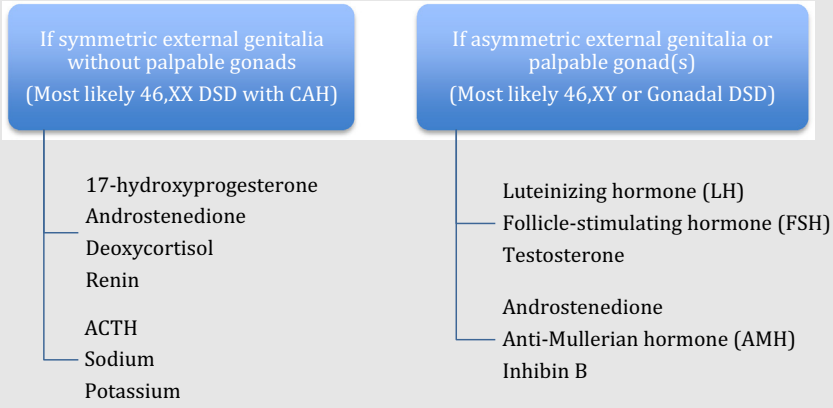
Table 1 – Assessment of the infant with genital ambiguity.

-History, including maternal
-Physical examination, including presence of a palpable gonad
-Karyotype with FISH for SRY
-Imaging of pelvis and lower abdomen including internal genitalia
-Basic hormonal testing



to determine whether or not the situation requires such expert evaluation promptly. Initial screening tests, together with history and physician examination findings, in most instances, provide adequate information to make a probable diagnosis (Table 1). However, this does not guide management when encountered in risky situations for which expert guidance is desperately needed. Hence, this article aims to provide guidance for initial workup and identify those risky situations in which expert guidance is needed.

Assessment of the 46,XX patient with adrenal hyperplasia assigned female or the 46,XY patient assigned male with mild-to-moderate hypospadias with testes would not be considered risky situations. Risky situations may present for such patients not only in the newborn, but also during childhood/adolescence or adulthood. Examples of risky situations in the newborn include as follows:

(1) Any situation in which there is consideration of removal of a well-developed male-type phallus.

Table 2 – Outcome information for specific diagnostic categories.

46,XX CAH	90% identify as female
46,XY cAIS	Almost all identify as female
46,XY pAIS	25% dissatisfied regardless of male or female assignment
5-α reductase deficiency	~70% identify as male
17 hydroxysteroid dehydrogenase	~50% of those assigned female self reassign male
46,XY cloacal exstrophy	88% identify as male
Ovotesticular DSD	Very limited data, variable outcome

(2) Consideration of a female assignment in any patient with a 46,XY karyotype with evidence of functional testicular tissue (except androgen insensitivity syndrome or LH-receptor defect).
(3) Assignment of male for any 46,XX patient.
(4) Any situation in which there is genital ambiguity and both ovarian and testicular development or gonadal dysgenesis for which extent of function is unclear.

Risky situations during childhood and adolescence would include any request for sex reassignment and development of cross-sex characteristics (virilization in a female, or feminization in a male). In an adult, evidence of possible gonadal tumor development would constitute a risky situation. In any risky situation, referral to a specialized center is indicated.

Medical history needs to determine parental consanguinity, and family history of salt-losing, unexplained infant deaths and genital anomalies, evidence suggestive of autosomal recessive disorders (e.g., steroid biosynthetic defects) or X-linked inheritance (e.g., androgen insensitivity syndrome), maternal virilization or possible medical or environmental disrupter exposure during pregnancy. A detailed description of the abnormalities of the external genitalia and the presence or the absence of gonads should be recorded using an appropriate classification.[2]

Communication with the parents and family should begin at the first encounter to acquaint them with the phenomena of genital ambiguity and the fact that there are no absolute bases to determine gender development, so there is always risk with sex assignment. It should be clarified that there is no single innate gender factor, genetic or otherwise, that provides prediction of gender development. Further, gonadal differentiation and karyotype do not always provide clear criteria. There are significant risks of overestimating the influence of neurobiological factors. While most sex