

Initial assessment of a baby with indeterminate sex

K S H de Silva¹

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Introduction

Since time immemorial, the birth of a healthy, normal baby has been the expectation of every parent. But sometimes identification of sex is difficult at birth when the baby is born with ambiguous genitalia. These disorders, formerly known as intersex disorders or true/pseudo hermaphroditism, are now known as disorders of sex development (DSDs) and defined as congenital conditions in which development of chromosomal, gonadal or anatomical sex is atypical¹. The profound psycho-social implications surrounding the birth of such a baby demands immediate attention with delicate and expert handling of the situation.

Implications of the clinical features

When the external genitalia are ambiguous, the baby is either a virilized girl or an undervirilized boy. The degree of ambiguity is defined using the Prader classification where the appearance of the external genitalia is described on a scale of stages 0 to 6². Stage 0 is the normal external genitalia of a girl and stage 6 is the appearance of a normal boy. External masculinization score (EMS) based on the external genital features is also used to describe the degree of ambiguity in an undervirilized boy².

Clinical differentiation of a virilized girl from an undervirilized boy is difficult. Expressing an opinion about the baby's sex should be avoided and all personnel responsible for the care of the baby should be vigilant not to inadvertently cause any further trauma to the already traumatized parents.

Virilization of a baby girl is commonly caused by excess fetal androgens resulting from congenital adrenal hyperplasia (CAH) or an excess of transplacental androgens^{3,4}. The commonest and most important condition is CAH due to 21 hydroxylase deficiency, in which the salt-wasting form is seen in

75% of babies^{4,5}. Early detection and institution of adequate treatment is essential in this potentially fatal condition.

Clinical features of a virilized baby girl with salt-wasting CAH

- Skin hyperpigmentation
- Systemic illness – hypoglycaemia, dehydration
- No palpable gonads
- Palpable cervix on rectal examination
- Cliteromegaly
- Posterior labial fusion ±
- Pigmented, rugose, labioscrotal folds

A baby boy will be undervirilized if there is inadequate production or end organ insensitivity to testosterone, the commonly seen conditions being partial gonadal dysgenesis (PGD), defects in the biosynthetic pathway of testosterone production or androgen insensitivity syndromes (AIS) such as partial androgen insensitivity (PAIS)^{3,4,6}.

If one or both gonads are palpable, the baby is more likely to be a boy but the absence of palpable gonads does not exclude the male gender. Pigmentation and dehydration with significant weight loss favours a diagnosis of salt-wasting congenital adrenal hyperplasia (CAH) in a baby girl. In experienced hands, a palpable cervix on rectal examination will indicate a female gender. A similar picture of a pigmented baby with ambiguous genitalia and dehydration with a significant weight loss may be seen in an undervirilized boy with the rare form of CAH due to 3 β hydroxysteroid dehydrogenase deficiency (3 β HSD). The clinical manifestations are variable due to the varying degree of deficiency of cortisol, aldosterone and testosterone^{5,6}.

¹Senior Lecturer in Paediatrics, Faculty of Medicine, University of Colombo.

Clinical features suggestive of a male gender in a baby with ambiguous genitalia

- Palpable gonad/s*
- Absence of pigmentation/dehydration*
- Absence of a palpable cervix on rectal examination

* Exception – under virilized boy with bilateral undescended testes

◆ Exception – 3 β HSD deficiency CAH

In the further clinical evaluation of an undervirilized boy, if the external genitalia are asymmetrical with only one gonad being palpable, it could be a normal or dysgenetic (streak) gonad or an ovotestis. If both gonads are palpable but the external genitalia are asymmetrical due to one being atretic and small, then PGD is the likely diagnosis as dysgenetic gonads are found in this condition. When both gonads are palpable and symmetrical and not atretic, then the possibilities for the ambiguity of the genitalia are PAIS or an androgen biosynthetic defect (due to 17β hydroxysteroid dehydrogenase deficiency)^{3,4,7}.

Trans-abdominal ultrasound scan by an experienced paediatric radiologist is extremely useful in the initial evaluation of such a newborn. If the uterus and ovaries are visualized, then the baby is a girl. But in PGD, as the gonads are dysgenetic, the production of both testosterone and anti Mullerian hormone (AMH) is deficient resulting in ambiguous genitalia and persistent Mullerian structures respectively. Therefore a rudimentary uterus could be identified ultrasonically in most boys with PGD^{3,4}. Mullerian structures could also be identified in a baby with ovotesticular DSD (formerly known as true hermaphroditism).

Clinical differentiation of an undervirilized boy

- Palpable gonad/s
- Asymmetrical external genitalia
- Presence of Mullerian structures

Gonadal dysgenesis with a Y chromosome Ovotesticular DSD

- Palpable gonads
- Symmetrical external genitalia
- Absent uterus

PAIS Testosterone biosynthetic defect

A karyotype is essential in the initial management. The fluorescent in-situ hybridization (FISH) technique to demonstrate the Y chromosome would be the ideal investigation as the results are available within 24 hours⁴. Unfortunately this investigation cannot be done in Sri Lanka. The procedure to obtain the results of a karyotype from peripheral blood lymphocytes takes up to one to two months. Although it is possible to identify the genetic sex based on clinical features alone, this could be very difficult and has, in the past, led to irrevocable damage with far reaching psycho-social implications being caused, albeit unwittingly, to the child and the parents. Therefore, till the karyotype result is available, examination of a buccal smear for the presence or absence of Barr bodies is a very useful preliminary investigation for the attending paediatrician to decide on further management of the baby and to start the long process of counselling the parents.

If the clinical suspicion is of a baby girl, with positive Barr bodies, as CAH is the commonest cause of ambiguous genitalia, the baby should be kept in hospital under observation for at least 2 weeks. The salt loss manifests after the 1st week of life^{3,7}. Therefore close monitoring of the serum electrolytes, blood sugar, weight and blood pressure is mandatory and a serum 17-hydroxy progesterone level done after the first few days of life will confirm the diagnosis along with the findings on trans-abdominal ultrasonography and changes in the serum electrolytes.

Estimation of serum testosterone, DHEAS, androstenedione and gonadotrophins may be helpful to determine the cause in an undervirilized baby boy.

Considerable progress has been made in identifying the molecular genetic basis for abnormal sex development^{1,6,7} but molecular genetic analyses are very expensive and cannot be done in Sri Lanka. Even with this advanced technology, a specific molecular diagnosis has been made only in approximately 20% of DSDs and a definitive diagnosis in only 50% of boys with DSDs¹.

Assignment of sex of rearing

Views differ in different countries regarding the timing of gender assignment, disclosure to parents and patient and the patients' rights regarding timing and extent of genital surgery^{6,7,8,9}. Against the cultural background of Sri Lanka, assignment of sex of rearing is probably best done as soon as possible and based on the decision taken by the parents. This

decision should be an informed one after several sessions of counselling including a detailed explanation about the possible short and long term implications of assignment to either sex. The chosen gender should give the patient the best possible chance of a happy childhood and adolescence, a secure gender identity and the ability to live a normal adult life with the potential for future fertility^{1,6,10}. To achieve this goal, the diagnosis, internal and external genital phenotype, surgical options, possibility of gonadal malignancy and need for lifelong replacement therapy should be considered^{1,3,8}.

Virilized baby girls with CAH are best brought up as girls with adequate replacement therapy and reconstructive surgery^{1,6,7,10}. When deciding the sex of rearing in an extremely undervirilized boy, pharmacological interventions such as a trial of testosterone and/or a hCG stimulation test could be performed to assist the parents to make the final decision^{6,7}. It is advisable not to register the birth of any baby with a DSD till the final decision regarding gender assignment has been made.

A multidisciplinary team approach to the management of these children is essential^{4,6}. Genetic counselling should be offered to the parents and the patients closely monitored through childhood to adolescence and thence to adulthood and render whatever assistance they need, whenever they need it, as disorders of sex development are conditions with lifelong implications.

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