Sexual ambiguity is a complex and often confusing medical problem in the newborn. Determining the appropriate sex in these patients is an urgent matter, particularly in congenital adrenal hyperplasia (CAH). On rare occasions, the cause of ambiguity remains unexplained despite extensive studies. The general appearance of the external genitalia is seldom diagnostic of the underlying disorder, but palpable gonads as a general rule exclude female pseudo-hermaphrodites. Treating a child with ambiguous genitalia continues to be one of the most challenging diagnostic as well as therapeutic problems. A multidisciplinary approach involving pediatric endocrinologists, neonatologists, pediatric surgeons, psychiatrists and social workers, is needed. Essential in the satisfactory management of these children is early diagnosis and gender assignment, which may have positive effects on the well-being of both child and family. However, recent reports of long-term follow-up of children whose gender was reassigned after surgical correction of their genital organs showed negative socio-psychological effects. This study describes the underlying causes for ambiguous genitalia in children seen over a ten-year period (1989-1999) at King Faisal Specialist Hospital and Research Centre, a tertiary care facility in Saudi Arabia.

**Patients and Methods**

We retrospectively reviewed a total of 120 medical records of patients with a primary indication of ambiguous genitalia that were referred to the cytogenetic lab for karyotyping during the period of 1989 to 1999. Diagnosis was based on karyotyping and on a clinical impression from the primary physician, who was primarily a staff pediatrician, endocrinologist and/or pediatric urologist. From these data, the precursor-to-product ratios were calculated for enzyme deficiencies of testosterone. 

This study describes the underlying causes for ambiguous genitalia in children seen over a ten-year period (1989-1999) at King Faisal Specialist Hospital and Research Centre, a tertiary care facility in Saudi Arabia.
one, dehydrotestosterone, dehydroepiandrosterone and androstenedione pathways. Genitogram and ultrasound were also done on some of the patients.

Results
Ambiguity attributed to endocrine causes was found in 63 patients (Table 1). CAH was the underlying cause in 41 of 63 patients, 39 of whom showed a 46,XX karyotype. Two cases were 46,XY (both 3 β-hydroxylase deficiency). Six patients had a clinical picture of vanishing testicular syndrome (VTS); 5 patients showed Leydig cell hypoplasia (LCH); androgen insensitivity syndrome (AIS) was seen in another 5 patients, 5 α-reductase deficiency was found in 3 patients, gonadal dysgenesis (histologically proven) in 2 patients, and panhypopituitarism in one patient. All of these patients showed a 46,XY karyotype.

In 56 patients ambiguous genitalia were due to congenital developmental defects (CDD) (Table 2). Ten patients had cloacal abnormality. Among these, 6 patients were 46,XY, and 4 patients showed 46,XX karyotype. Another ten patients had congenital local genital malformation; 9 of these cases showed a 46,XY karyotype and the remaining a 46,XX complement. Hypospadias was seen in 11 patients, and all of these showed 46,XY karyotype. Twenty-six patients were classified differently for various reasons. Eight patients had ambiguity as part of their syndrome, including trisomy 13 (2 cases), split notochord syndrome (2 cases), Opitz syndrome (1 case), CHARGE association (1 case), Prader-Willi syndrome (1 case), and Sanjad-Sakati syndrome (1 case). Nine patients with ambiguity had dysmorphic features of non-specific syndromes, with associated metabolic disease in 2 cases (Table 2). The karyotype analysis in these cases is shown in Table 2. Seven of these cases were classified as idiopathic and of these, 6 showed 46,XY and one showed 46,XX karyotype. The cause of ambiguous genitalia could not be identified despite extensive clinical and laboratory investigations.

Age of presentation, consanguinity and family history are shown in Table 3 for patients with endocrine defects and in Table 4 for patients with CDD. Age of presentation in both categories was less than 18 months in more than 85% of patients. Consanguinity, mainly first cousin, ranged between 60% and 100% in various types of endocrine and CDD defects. A family history of ambiguous genitalia in endocrine defects was present in all patients except in cases with 5 α-reductase deficiency and vanishing testicular syndrome. In CDD, a family history of ambiguous genitalia was reported only in patients with hypospadias.

Table 5 summarizes data on the 15 patients whose gender was reassigned at birth or at diagnosis. Eight patients with CAH due to 21-hydroxylase deficiency presented as males, four of whom were reassigned as females based on 46,XX karyotype. The parents of the other patients declined to change the sex of their child. One male patient with 11 β-hydroxylase deficiency was reassigned as a female (46,XX) and another female patient with 3 β-hydroxylase deficiency declined to have the gender reassigned as male based on the presence of an XY karyotype. Of 3 female patients with 5 α-reductase deficiency, two were reassigned as 46,XY males, and the other declined. One female patient with partial AIS was reassigned as a male and, another male patient with cloacal anomaly as a female.
Table 3. Age of presentation, consanguinity and family history in patients with endocrine related ambiguous genitalia.

| Disorder                      | (No. of cases) | Age at presentation | Consanguinity* | Family history of ambiguous genitalia |
|-------------------------------|----------------|---------------------|----------------|--------------------------------------|
|                               |                | < 18 months      | >18 months     |                                      |
| CAH                           |                | 30               | 3              | 23                                   | 10                                   |
| (i) 21-OH (33)                |                | 3                |                | 23                                   |                                      |
| (ii) 11B-OH (6)               |                | 3                |                | 4                                     | 3                                     |
| (iii) 3B-OH (2)               |                | 2                |                | 2                                     | 1                                     |
| 5 α-Reductase (3)             |                | 3                |                | 3                                     | 0                                     |
| Vanishing testis syndrome (6) |                | 5                |                | 1                                     | 5                                     | 0                                     |
| Leydig cell hypoplasia (5)    |                | 4                |                | 1                                     | 5                                     | 5                                     |
| Androgen insensitivity Syndromes (5) | | 4 | 0 | 5 | 1 | 1 |
| Gonadal dysgenesis (2)        |                | 0                |                | 2                                     | 0                                     | 2                                     |
| Panhypopituitarism (1)        |                | 1                |                | 0                                     | 1                                     | 1                                     |
| Total (63)                    |                | 52               | 11             |                                       |

*Majority were first cousins.

Table 4. Age of presentation, consanguinity and family history in patients with congenital developmental defects.

| Disorder                          | (No. of cases) | Age at presentation | Consanguinity* | Family history of ambiguous genitalia |
|-----------------------------------|----------------|---------------------|----------------|--------------------------------------|
|                                   |                | < 18 months      | >18 months     |                                      |
| Cloacal abnormality (10)          |                | 9                  | 1              | 2                                     | 0                                     |
| Congenital local genital anomaly (10) |            | 9                  | 1              | 2                                     | 0                                     |
| Hypospadias (11)                  |                | 10                 | 1              | 4                                     | 2                                     |
| Metabolic defects (2)             |                | 2                  | 1              | 2                                     | 0                                     |
| Syndromes (8)                     |                | 7                  | 1              | 4                                     | 0                                     |
| Dysmorphic features (9)           |                | 8                  | 1              | 8                                     | 0                                     |
| Idiopathic (7)                    |                | 6                  | 1              | 3                                     | 0                                     |
| Total (57)                        |                | 51                 | 6              |                                       |

*Majority were first cousins.

Table 5. Gender assignment at and after diagnosis.

| Disorder                          | At presentation | Reassigned as | Decline | Assigned after diagnosis (XX) |
|-----------------------------------|-----------------|---------------|---------|-------------------------------|
|                                   | Female | Male | XX | XY |
| Congenital adrenal hyperplasia    |        |      |    |    |
| 21-OH deficiency                  | 8      | 4    | 4  | 9  |
| 11-BOH deficiency                 | 1      | 1    |    |    |
| 3 B-OH deficiency                 | 1      |      | 1  |    |
| 5 α-reductase                     | 3      | 2    | 1  |    |
| Androgen insensitivity            | 1      |      | 1  |    |
| Cloacal anomaly                   | 1      | 1    |    |    |
Discussion

A genetic female with sexual ambiguity—also known as female pseudohermaphroditism (FPH)—accounts for 50% to 70% of endocrine causes of sexual ambiguity. These individuals possess ovaries with masculinized genitalia, generally due to CAH and rarely as a result of maternal ingestion of androgenic compounds or a virilizing tumor during pregnancy. In our series, 62% of the cases with ambiguous genitalia were FPH, and CAH was diagnosed in all of these patients (21β-hydroxylase deficiency was present in 84.6% and 11β-hydroxylase deficiency in 15.4% of cases). Previous studies from Saudi Arabia reported a higher frequency of 11β-hydroxylase deficiency (25.6%). The difference between our study and the previous study might be due to sample size (41 patients in the present study versus 86 patients in the previous study). Both studies were hospital-based and may not reflect the general population incidence or prevalence of CAH and its cause; however, our data on FPH and CAH is similar to previous reports in the literature. All patients with CAH who were expected to be a female were found to have a 46,XX karyotype, except in two patients with 3β-hydroxysteroid dehydrogenase deficiency, who were found to have 46,XY karyotype.

Male pseudo-hermaphrodites (MPH), or genetic males characterized by the presence of female or ambiguous genitalia, have testes and their sex chromosomes are XY. They do not have Mullerian duct structures. The undervirilization of the external genitalia in these patients is due to inadequate exposure to androgen during the first trimester. Patients with 5α-reductase deficiency, LCH due to inadequate or absent testosterone, and AIS are examples of MPH in this study. VTS followed by LCH and AIS constituted the majority of MPH cases in this study. AIS is considered a common cause of ambiguity in a genetic male, but it manifests in a wide spectrum of defects in male sexual development, ranging from complete female phenotype to a phenotypically normal infertile male. In prepubertal children, LH secretion is physiologically decreased; therefore, testosterone production is assessed after HCG stimulation, which results in a rise in testosterone concentration. Five cases presenting in this study were diagnosed by routine methods since molecular analysis was not available. This disorder is the result of mutations of the androgen receptor gene. Molecular screening using single-strand conformation polymorphism is currently used in the diagnosis.

Recently, Holterhaus et al reported that the same mutation in the androgen receptor gene (AR) is responsible for variable external genitalia in different patients. Furthermore, when the mutation showed in a family of four members displaying variable external genitalia, the AR gene function could be switched from subnormal to normal in the presence of a physiological concentration range of testosterone. Based on their observations, they concluded that the variability observed in AIS patients is due to the time-dependant variation in testosterone concentration in early fetal development and its impact on the mutant AR gene function.

Hypospadias is found commonly in newborn boys and is seen in approximately 8.2/1000 live births. It may be inherited as a Mendelian defect, but is mostly an isolated finding. In our series, eleven patients presented with hypospadias, including two who gave a positive family history of hypospadias. In cases with severe hypospadias but fully descended testes, a testosterone biosynthetic defect has been reported in approximately 5%. In one study, 50% of boys with proximal hypospadias and fully descended testes were shown to have evidence of a testosterone biosynthetic defect with a high incidence of 3β-hydroxysteroid dehydrogenase and lyase deficiency. Since endocrine evaluation in our patient was not done, the question of testosterone biosynthetic defects in our population remains unanswered.

Cloacal anomaly may be present as ambiguous genitalia, generally associated with a higher predilection for extrophy and epispadias, in males more than in females (2:1). In our series, the ratio was 1.5:1. Patients often show variable malfunction of the cloaca, and generally present with a difficult reconstructive challenge for the pediatrician, urologist and surgeon. In boys, the penis tends to be short and stubby with dorsal curvature, whereas girls have a bifid clitoris. Some patients with cloacal anomalies might have additional defects, including myelomeningocele, hydrocephalus, cardiac, renal, gastrointestinal and limb defects. The diagnosis should be suspected in any female fetus presenting with bilateral hydronephrosis, a poorly visualized bladder and a cystic lesion arising from the pelvis antenatally. In seven patients in our study with ambiguous genitalia, endocrine defects could not be found. Six of these cases turned out to
be 46,XY karyotype and one patient was 46, XX karyotype. Single gene defects may be a cause in these cases.

Reassignment of sex in patients with ambiguous genitalia is a very sensitive matter. The topic has been debated extensively and specific guidelines are proposed to manage cases of traumatized or ambiguous genitalia. These guidelines take into consideration how the patient will develop post-puberty and adapt as a sexually active person. Accordingly, rearing as males is recommended in 1) 46,XY patients with partial AIS, 2) hypospadias, 3) micropenis with testes, because these children should develop a satisfactory male gender identity and sexual function; and 4) 5 alpha-reductase deficiency. Rearing as females is recommended in 1) XY patients with complete AIS; 2) XX or XY patients with gonadal dysgenesis; 3) 46,XX patients with CAH with testes, because these children should develop a satisfactory male gender identity and sexual function; and 4) 3 patients with partial AIS, 2) hypospadias, 3) micropenis with androgen insensitivity. J Clin Endocr Metab. 1978; 46:1-7. Martinez-Mora J, Saz JM, Torn A, et al. Male pseudohermaphroditism due to Leydig cell agenesis and absence of testicular LH receptors. Clin Endocrinol. 1991; 34: 485-491. Schwartz M, Imperato-McGinley J, Peterson RE, et al. Male pseudohermaphroditism secondary to an abnormality in Leydig cell differentiation. J Clin Endocrinol Metab. 1981; 53:123-127.

In conclusion, newborns with ambiguous genitalia pose a difficult emotional situation for parents in deciding their future sexual orientation. Moreover, these parents also face a social nightmare explaining to their relatives and friends, the gender reassignment. The physician managing these families could minimize the trauma of having a child of unidentified sex by providing appropriate genetic counseling so that the parents can make an early decision. Prenatal DNA testing in at-risk families should be considered, and appropriate therapy offered to minimize or prevent genital ambiguity.

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