Ambiguous Genitalia

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In the delivery room, most health care professionals usually do not have any problems in determining the sex of the newborn infant

However, once in every 4500 births, an infant may have an ambiguous external genitalia which can result in difficulties in proper sex assignment.[1] Ambiguous external genitalia in a newborn infant can be the result of virilisation of a female, incomplete masculinisation of a male or a true hermaphrodite. In order for a paediatrician to investigate, manage such a patient, and give effective counselling to the parents, a proper understanding of the physiology of sexual differentiation, causes of ambiguous sexual development and their genetic basis is essential.

Normal Sexual Differentiation

The genetic material present in the Y chromosome is crucial to the differentiation of the fetus into the male phenotype. Available evidence suggests that the testes-determining sequence known as the sex-determining region of the human Y chromosome (SRY) is located on the short arm of the Y chromosome adjacent to the pseudo-autosomal region. This 14Kb gene, which encodes a product thought to function as a DNA-binding transcription factor, is essential for testicular development.[2] It is possible that SRY initiates testis development through interaction with other genes, some of which will be involved in regulation while others will be downstream targets of SRY. The differentiation of the gonadal ridge into testis occurs around 7 to 8 weeks' gestation under an influence of SRY. Male phenotypic differentiation is dependent on the action of 3 hormones, anti-Mullerian hormone (AMH), testosterone and dihydrotestosterone (DHT). AMH which is produced by Sertoli cells of the fetal testis, causes regression of the Mullerian ducts. The AMH gene has been mapped to the short arm of chromosome 19 and has 5 exons that code for a mature protein of 535 amino acids.[3] Testosterone secreted by the fetal Leydig cells stimulates the growth and differentiation of the Wolffian ducts into the epididymis, vas deferens and seminal vesicles.

Testosterone is converted to DHT by the enzyme 5α-reductase present in the urogenital sinus and external genital anlagen. The development of the prostate, prostatic utricle, scrotum, penis and the male type urethra is mediated by DHT. Both DHT and testosterone exert their effects by binding to the androgen receptor. The androgen receptor gene is found on the X chromosome and consists of 8 exons and an androgen binding and a DNA-binding domain similar to other steroid receptors.[4] Two 5α-reductase genes have been identified. The type 1 isoenzyme is encoded by a gene on chromosome 5 and the type 2 isoenzyme is encoded by a gene on chromosome 2.[5] Only mutations in the type 2 gene are responsible for clinical manifestations of 5α-reductase deficiency.

The control of testosterone secretion by the fetal testes between 8 to 12 weeks' gestation remains unclear and it is likely that testosterone secretion occurs independent of pituitary gonadotropin stimulation during this period. After 13 weeks' gestation, testosterone secretion and penile growth are regulated by pituitary luteinising hormone (LH) and human chorionic gonadotropin (HCG) present in the fetal circulation. Fetal testosterone secretion peaks at about 20 weeks' gestation and then progressively falls towards late gestation coinciding with the decline in LH and HCG in the fetal circulation. In humans, descent of the testes into the scrotum during the second and third trimester, is required to allow for complete spermatogenesis. A biphasic model of testicular descent has been proposed. The gubernaculum and epididymis play an important mechanical role in the first phase of transabdominal descent with AMH suggested as the important hormonal mediator. The second transinguinal phase of testicular descent depends on testosterone-mediated processes including dilatation of the inguinal canal, regression of the gubernaculum, growth of the vas deferens and scrotum, working synergistically with a progressive rise in intra-abdominal pressure with increasing gestation.[6] The testes have descended into the

scrotum in 97.3% of term infants, 79% of preterm infants and 99% of 1-year-old infants.

In the absence of SRY, rudimentary ovarian development occurs between 6 to 8 weeks' gestation. The Wolffian ducts degenerate and the Mullerian ducts serve as the anlagen of the uterus, fallopian tubes and the upper two-thirds of the vagina. Although ovarian development has been thought to occur by default in the absence of SRY, recent evidence suggests that a locus termed dosage sensitive sex reversal (DSS) on the short arm of X chromosome may be a specific gene promoting differentiation into the female phenotype.[7]

Female Pseudohermaphrodite

The common causes for female pseudohermaphroditism are shown in table I. Steroid 21-hydroxylase (P450c21) deficiency accounts for over 90% of the cases of congenital adrenal hyperplasia (CAH) diagnosed in the neonatal period with 60% of the patients presenting with salt loss. The condition can be diagnosed by elevated 17-hydroxyprogesterone (170HP) levels in the blood 48 hours after birth. The two P450c21 genes (CYP21P and CYP21) have been mapped to chromosome 6 and only CYP21 is actively transcribed with CYP21P being a pseudogene.[8] 21-hydroxylase deficiency can be due to gene deletion, gene conversion or point mutations and recent mutational analysis has shown that gene deletion or conversion are uncommon in Southern Chinese with 21-hydroxylase deficiency.[9] 11-hydroxylase and 3β-hydroxysteroid dehydrogenase (3βHSD) deficiencies are rare. Female patients present with virilisation and increased pigmentation. Hypertension is found in 11-hydroxylase deficiency and plasma 11-deoxycortisol level is elevated but salt loss and hypotension are found in the other 2 forms of CAH.[8]

Exposure of mothers of female infants to androgens and progestogens at 6 to 10 weeks' gestation can result in posterior fusion of the vagina, scrotalisation of the labia and clitoral enlargement. Androgen exposure after this critical period will usually only result in clitoral enlargement. Rarely, teratologic conditions can result in genital ambiguity in females.

TABLE I. Causes of female pseudohermaphroditism

Congenital adrenal hyperplasia
21α-hydroxylase (P450c21) deficiency
11β-hydroxylase (P450c11) deficiency
3β-hydroxysteroid dehydrogenase deficiency
Exposure of mothers of female infants to androgens and progesterone
Progestogens, testosterone, danazol
CAH, virilising adrenal or ovarian tumours, luteoma, luteal cyst of pregnancy
Teratologic conditions associated with other congenital malformations of the lower intestine and urinary tract

TABLE II. Causes of male pseudohermaphroditism

Gonadal dysgenesis
Testosterone biosynthetic defects
20, 22-desmolase (P450SCC) deficiency
3β-hydroxysteroid dehydrogenase deficiency
17α-hydroxylase (P450c17) deficiency
17,20-lyase (P450c17) deficiency
17-ketosteroid reductase deficiency
Androgen resistance syndrome
5α-reductase deficiency
Associated with multiple congenital abnormalities, e.g. lethal acrodysgenital dwarfism, camptomelic dwarfism, Nagjar syndrome, Drash syndrome
Leydig cell unresponsiveness to human chorionic gonadotrophin
Idiopathic

True Hermaphrodite

Hermaphroditism is a rare cause of ambiguous genitalia when both ovarian tissue containing ovarian follicles and testicular tissue showing distinct tubules, are present in the same individual. The condition appears to occur more frequently in Africa and Europe. The most common karyotype found is 46XX which occurs in 70% of reported patients.[10] Various combinations of testes, ovary and ovotestis have been found. The clinical manifestations and hormonal profile depend on the amount of functioning gonadal tissue. Ovarian tissue frequently functions normally in hermaphrodites but fertility is rare.

Male Pseudohermaphrodite

The common causes of male pseudohermaphroditism are shown in table II. Gonadal dysgenesis can be classified according to the karyotype and gonadal histology and can be partial or complete. Most patients with partial XY gonadal dysgenesis have varying degree of genital ambiguity depending on the amount of functioning testicular tissue present. As the dygenetic gonad secretes inadequate or no AMH, most children with XY gonadal dysgenesis are found to have hypoplastic Mullerian structures. The risk of malignant change in the dysgenetic gonad is

high especially in the presence of all or even part of a Y chromosome.[11]

Testosterone biosynthetic defects lead to inadequate androgen production by the testes during the critical period of fetal sexual differentiation. The first 3 enzyme defects are found in both the adrenal gland and testes while 17,20 lyase and 17-ketosteroid reductase are only found in the testes (table II). In P450SCC deficiency, there are low levels of all steroid hormones and severe salt wasting. In 3β-HSD deficiency, DHEA is elevated in the presence of glucocorticoid and aldosterone deficiency. In 17-hydroxylase deficiency, 170HP level is low and excessive production of salt-retaining steroids like deoxycorticosterone and corticosterone leads to hypertension. In patients with 17,20 lyase deficiency, the serum testosterone, androstenedione and DHEA levels are low but the 170HP level is elevated. Elevated androstenedione and low testosterone concentration basally and after HCG stimulation is suggestive of 17-ketosteroid reductase deficiency. Mullerian structures are absent in these patients as the production of AMH is unaffected.

No obvious cause for the genital abnormality can be found in up to 40% of the male pseudohermaphrodites

Deficiency in 5-α-reductase with the resultant decrease/absent dihydrotestosterone causes a discordance between Wolffian structure development (testosterone responsive) and the external genitalia and urogenital sinus (DHT-dependent) differentiation. Except for the prostate (also DHT-dependent), internal genital organs including vas deferens, seminal vesicle and epididymis are normally developed. The external genital phenotypes vary with pseudovaginal perineoscrotal hypospadia being the commonest. Circulating DHT level is disproportionally low compared with testosterone, which is more obvious during neonatal/early infancy and after puberty when testosterone synthesis becomes active. One classical finding in these patients is the significant virilisation at puberty with phallic enlargement, deepening of voice and descent of testes secondary to very high testosterone levels.

Impaired androgen sensitivity results from a range of quantitative or qualitative defects in the androgen receptor. With complete insensitivity the external genitalia will be unambiguously 'female'. For partial insensitivity, the external genital phenotypes are heterogeneous and exhibit no general correlation to the individual molecular pathologies. The most common phenotype is perineoscrotal or penile hypospadias, a small vaginal pouch, a hooded phallus and preputial folds unfused ventrally and occasionally lifid scrotum containing gonads. Elevated LH and testosterone levels are expected as well as poor penile growth in response to exogenously administered testosterone. In post-pubertal patients, gynaecomastia is a usual feature.

Leydig cell unresponsiveness to HCG results in male pseudohermaphroditism with cryptorchidism, hypoplasia of Wolffian ducts and absence of Mullerian structures. The serum testosterone is low and remains low after HCG stimulation. The serum gonadotrophin concentrations are elevated. Testicular biopsy reveals an absence of Leydig cells but a normal number of Sertoli cells.

Ambiguous external genitalia may be seen in patients with multiple congenital abnormalities (table II). Newborn infants with Drash syndrome present with genital ambiguity, nephrotic syndrome due to a congenital nephropathy, Wilm's tumour and testicular dysgenesis. Another related syndrome consisting of Wilm's tumour, aniridia, genital abnormality and mental retardation (WAGR syndrome), is associated with deletion of the short arm of chromosome 11 (11p13). However, despite extensive investigations, no obvious cause for the genital abnormality can be found in up to 40% of the male pseudohermaphrodites. It is possible that some of these patients may have defects of gonadotrophin structure or timing of the development of gonadotrophin receptors.

Assessment of Patients with Ambiguous Genitalia

The medical history may be revealing if there is a history of maternal virilisation or exposure to androgenic substances during pregnancy. Family history of genital ambiguity, sudden neonatal death and consanguinity are also important. During the physical examination, the extent of the genital abnormality should be recorded in detail: size of phallus and abundance of erectile tissue, presence of chordae and whether there is a common urogenital opening. If a gonad is palpable, it is likely to be a testis and implies a male chromosomal make up. Skin pigmentation in an ill newborn with signs of dehydration and ambiguous genitalia will suggest salt-losing forms of CAH. Attention should also be paid to the presence of dysmorphic features and other associated anomalies.

The laboratory work-up of patients with ambiguous genitalia is mainly to determine the genetic sex, delineate the gonadal and genital structural components, document the integrity of the steroid (gonadal or adrenal) biosynthetic pathway and demonstrate the responsiveness to androgens. The extent of such work-up required for gender assignment is different from that needed for the ultimate aetiologic diagnosis. In fact, the practical clinical approach to

ambiguous genitalia has not changed much despite our enhanced understanding of sex determination and differentiation, and the explosion of knowledge about individual molecular pathologies involved. This is partly because many methods involved in reaching the final diagnosis cannot be readily adopted as regular clinical laboratory tests due to their complexity and cost, and partly because of the lack of immediate management implication of such knowledge in the individual patient. Nevertheless, the potential practical implications of these new advancements should not be underestimated when these become more generally mastered and more practical methods are developed.

TABLE III. Molecular biology techniques employed

1. Study tissue/cell derived DNA or polymerase chain reaction (PCR) amplified gene fragments for mutation by cloning, Southern blot hybridisation using gene specific probes or allele specific oligonucleotide, single-strand conformation polymorphism (SSCP) or direct sequencing
2. Study the mRNA transcripts using reverse transcriptase polymerase chain reaction (RT-PCR), Northern blot hybridisation or RNase protection assay
3. Production of mutant species (e.g. androgen receptor) *in vitro* for functional (e.g. binding to ligand or specific DNA sequence) or analytical studies (e.g. immunoblotting)
4. Functional (*ex vivo*) assay using gene-reporter constructs, e.g. DNA sequence encoding androgen receptor responsive elements linked with a readily measurable reporter (luciferase) system; these constructs are then introduced into the skin fibroblast from individual patients for assessing the functional integrity of the androgen receptors

Primary sex determination does not guarantee normal secondary sex differentiation

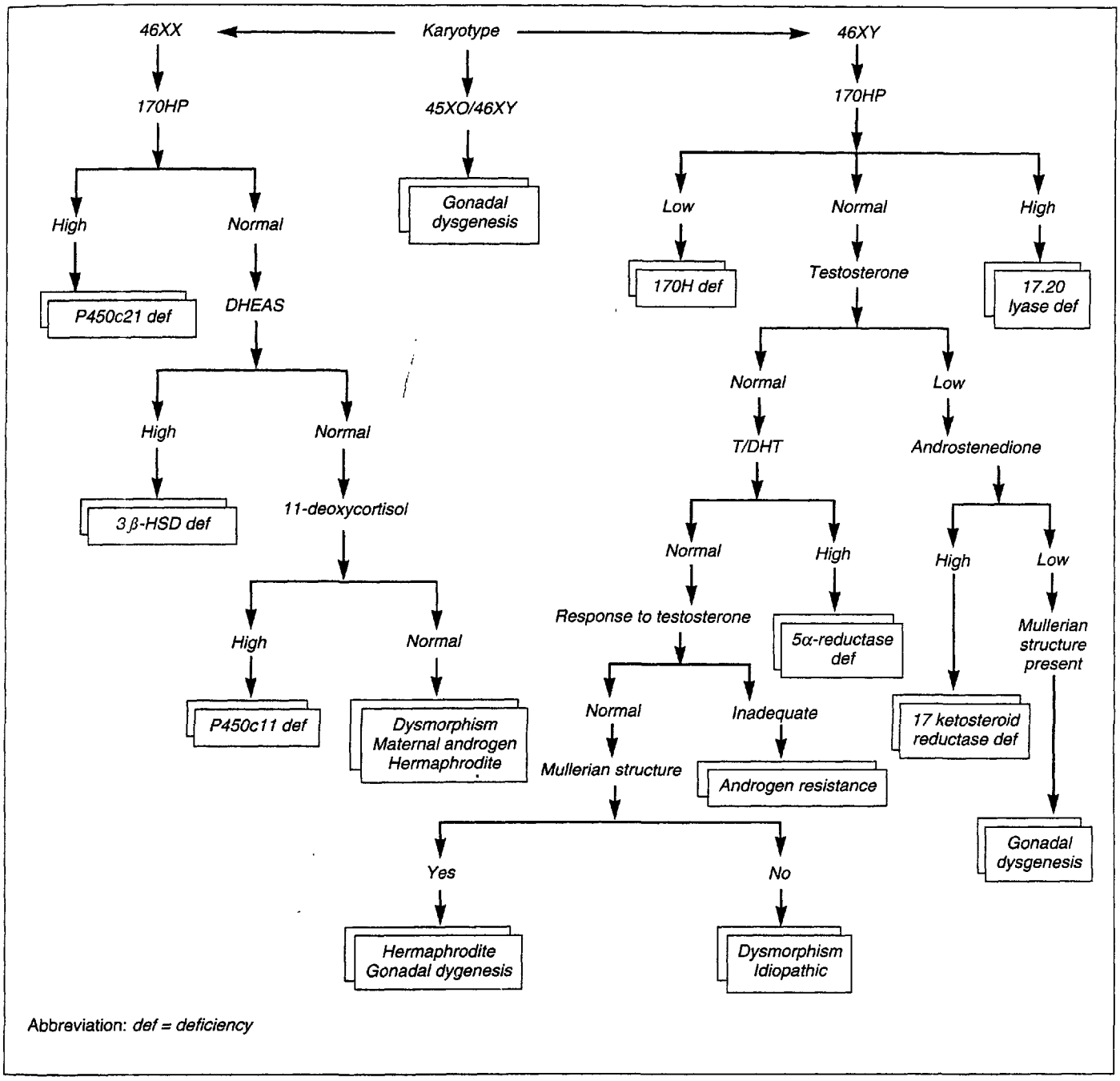
Primary sex determination does not guarantee normal secondary sex differentiation, and so careful analysis of the discordance between the genetic sex and the gonadal/genital phenotypes of a patient often provide the likely differential diagnoses and is essential in deciding which diagnostic tests to be performed. The detection of Y-chromosomes by classical cytogenetic methods generally imply the presence of SRY, unless its inheritance is defective as in some XX males and XY females. When indicated, more refined methods are available to specifically identifying the SRY genes. Gonadal and genital structures (gonads, Mullerian structures, prostate, urogenital sinus) assessment are facilitated by transabdominal (or even transrectal) ultrasonography and magnetic resonance imaging, genitography, panendoscopy, laparoscopy and, when indicated, gonadal biopsy (e.g. in an infant suspected to be a true hermaphrodite or have gonadal dysgenesis). This information is also very important for planning surgical reconstruction when deemed necessary.

Biochemical assays of the basal and/or stimulated hormones in various combinations will provide a diagnosis responsible for the majority of clinical patients encountered. It is, however, important to remember that the neonatal hypothalamo-pituitary-gonadal axis is active and lasts up to 3 to 6 months and so basal hormonal levels can be very revealing. Thus, elevated basal LH and FSH with very low testosterone will indicate lack of functional testicular tissue. Increased testosterone *per se* will be compatible with androgen insensitivity. Beyond this period, an HCG stimulation test may be necessary. Elevated precursors proximal to and deficiency in hormones distal to an enzymatic step in the steroidogenesis pathway implies a block at that level, e.g. elevated 17-hydroxyprogesterone:cortisol ratio in P450c21 deficiency; increased DHEA:androstenedione ratio in 3-β-hydroxysteroid dehydrogenase deficiency; increased 17-OH-pregnenolone:dehydroepiandrosterone (DHEA) in P450c17 deficiency; increased testosterone:-dihydroxytesterone ratio in 5-α-reductase deficiency. Again stimulation test using ACTH or HCG may help in bringing out more subtle derangement. Except for 5-α-reductase assay using the genital skin fibroblast culture, direct assessment of individual enzyme activity is not feasible since the relevant tissues are usually not available. *In vivo* testosterone responsiveness could be demonstrated by assessing the response of the phallus size to exogenous testosterone enanthate 25mg given intramuscularly every month for 3 doses. A proposed flow chart for the investigation of a patient with ambiguous external genitalia is shown in the Practice Guide on page 9.

Lastly, a number of molecular biology techniques have been used to study patients with ambiguous genitalia (table III). Detailed discussion of each individual technique is beyond the scope of the present article but every effort should be made to understand the principles and take advantage of the versatile methods already available, and yet more to come. Most commonly, these methods are employed to delineate a specific genetic defect, using analysis of DNA extracted from peripheral leucocytes or any tissue available. However, whereas gross deletion or change resulting in frame shift with obvious disruption of the gene product must affect its function(s), such minor change as single nucleotide substitution may or may not.

JPOG Practice Guide

Diagnostic Flow Chart for a Patient with Ambiguous External Genitalia



Abbreviation: *def = deficiency*

TABLE IV. Known genetic defects P450c21 deficiency, 5-α-reductase deficiency and androgen insensitivity

	P450c21	5-α-reductase	Androgen receptor
Deletion	CYP21 + C4 gene	All 5 exons (> 20kb) Just 2bp – frameshift	In-frame deletion – exon 3
Duplication	CYP21 + C4 gene	–	–
Insertion	Frameshift	–	–
Gene conversion	Change the entire CYP21 to CYP21P	–	–
Single nucleotide substitution	Amino acid substitutions	Amino acid substitutions (in all 5 exons)	Amino acid substitution (mainly) ligand binding domain, but also DNA binding domain)
	Abnormal splicing (intron 2)	Abnormal splicing (intron 4)	Abnormal splicing
	Premature termination		Premature termination

Therefore, in order to demonstrate the functional significance of some mutations, it is more desirable to analyse the mRNA encoding adrenal/gonadal tissue specific proteins which unfortunately are rarely accessible (as for direct enzyme assays mentioned above). This can, however, be circumvented by methods like *in vitro* expression of patient-specific mutation gene in artificial system, providing the gene products (RNA or protein) for analysis. Unlike identifying simple DNA mutations, such approach is obviously very labour intensive and has a lot of technical limitations, and is thus precluded from being used as routine assay. Nonetheless, as research tools, these elaborate methods are essential in establishing the causal role of certain mutations which can then be identified with relative ease in most modern clinical laboratories. A list of the range of molecular defects reported for 21 hydroxylase, 5-α-reductase and androgen receptor is also presented in table IV. Similar molecular mechanisms and pathologies may affect other genes encoding key proteins/factors in sexual determination and differentiation. All the enthusiasms about knowing the genetic diagnoses aside, good clinical sense must be exercised in selecting appropriate patients for these tests to make their applications effective and efficient.

Management of Patients with Ambiguous Genitalia

Female patients with congenital adrenal hyperplasia should be given appropriate steroid replacement once the diagnosis is made. Recession clitoroplasty, perineoplasty, and vaginoplasty should be performed before 18 months of age. In male pseudohermaphrodites, decision on the sex of rearing is a daunting task for the attending paediatrician. The chromosome result is important but it has no bearing on the sex of rearing. In most centres, the female sex of rearing is usually favoured. If the male sex of rearing is considered, the phallus should be of adequate size with presence of erectile tissue. Testosterone responsiveness must be established and one should also take into account the views and cultural background of the parents. A patient assigned a male sex should be able to urinate standing up and have normal sexual function in adulthood after surgical correction of the genital abnormality.

The parents must be counselled and fully informed and actively involved in the assessment and the sex assignment. The help of an experienced clinical psychologist in this field may be indicated. Once the diagnosis has been reached, the parents should be referred for genetic counselling if the cause of genital ambiguity in the newborn is due to an inherited disorder. Prenatal diagnosis and prenatal treatment (e.g. prenatal treatment of a fetus with P450c21 deficiency to prevent genital abnormality) can be offered to the parents in some of the conditions.[12]

In a male pseudohermaphrodite assigned to the female sex of rearing, recession clitoroplasty, and gonadectomy should be performed in infancy or early childhood. Puberty has to be induced at an appropriate age.

The patients usually go through a difficult adolescent period and psychological and emotional support and counselling to both parents and patients are important aspects of management during adolescence. Genital reconstruction should be performed by an experienced gynaecologist after the patient is fully grown. As the risk of malignancy is high in gonadal dysgenesis, patients assigned to the male sex of rearing, a testicular biopsy should be performed and the specimen examined for evidence of carcinoma *in situ* (CIS). If CIS is present, the testis should be removed. If CIS is absent, a repeat biopsy should be performed after puberty. In childhood, the testes should be regularly examined and investigated with ultrasound and assays for α-fetoprotein and HCG.

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Treatment of Candidosis

Treatment must involve both mother and infant in order to avoid 'ping-ponging' of the candidosis between the two. Malpositioning must be corrected.

Eradication of *Candida*

The mother should be treated with non-absorbable oral antifungal agents for several weeks or until symptoms have disappeared. The object is to lower the population of *Candida* in the gut and thence the skin.

Topical antifungal treatment is necessary for nipple thrush. Nystatin ointment, 4 times daily, is useful and miconazole gel is popular, although the latter may itself cause irritation.

The baby is best treated with miconazole oral gel, one-quarter spoon 4 times daily after feeds, rubbed onto any obvious thrush in the mouth, for 5 days. Nystatin oral drops, 1ml 4 times daily, are less effective.

Replacement of Bacterial Flora

Lactobacillus acidophilus and bifidobacterium can be eaten as plain yoghurt (1 cup daily) or taken in powder or capsule form 3 times daily.

Diet and Lifestyle

The inclusion of refined carbohydrate and yeast-containing foods in the diet should be restricted. Many women report recurrence of symptoms within hours of ingestion of sweets or yeasted breads, etc. Maintenance of a balanced diet, high in unrefined carbohydrates and unprocessed foods, seems to improve long-term control of candidosis once medication is ceased.

Good self-care is also important. Many new mothers will often forget their own needs and exhaust themselves. They should be reminded to eat, drink, rest and exercise moderately, as far as is compatible with their levels of support, etc.

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