Complications of Ambiguous Genitalia: Causes, Prevention and Management

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Abstract: Incorrect diagnosis, incomplete investigations and improper surgical reconstruction can lead to complications in the management of patients with disorders of sex development. In this review we present examples and strategies to avoid these problems.

Keywords: Androgen sensitivity syndrome, Congenital adrenal hyperplasia, Disorders of sex development, Mixed gonadal dysgenesis, Ovotesticular DSD

Received: 4 December 2014 / Accepted: 19 December 2014

Introduction

Numerous complex entities cause Disorders of Sex Development (DSD), therefore, complications could be the result of errors in diagnosis, inappropriate sex assignment, inadequate or incorrect medical management, improper reconstruction and insufficient understanding and resolution of psychological issues. Problems are often preventable, many others can be treated, however, some problems can not be resolved at this time.

Incorrect Diagnosis

It is crucial that the initial physical examination of the baby with DSD be thorough. One must first identify patients in whom genital ambiguity is due to anatomic abnormalities which could be urologic in origin (epispadias, extrophy of the bladder or cloaca), genital (micropenis, penoscrotal transposition, "doughnut" scrotum), or perineal (absent phallus, caudal regression). Disorders of Sexual Differentiation are the result of three basic problems:

1. abnormal gonadal development e.g. mixed gonadal dysgenesis (MGD) and ovotesticular DSD
2. virilization of the female fetus or 46XX DSD
3. feminization of the male fetus or 46XY DSD

It is important to remember that Mullerian regression in the fetus only occurs if the testes produce Anti Mullerian Hormone (AMH) i.e. only in XY DSD. Patients with MGD, ovotesticular DSD and 46XX DSD all have uteri. The "cigar-shaped" uterus can be palpated through the anterior rectal wall and mucus can be milked towards the perineum in the perinatal period. Secondly, testes and ovotestes tend to descend into the groin and even into the labioscrotal area whereas ovaries do not. Thus 46XY DSD patients have palpable gonads in both groins while in MGD and ovotesticular DSD, the groins and labioscrotal areas are asymmetric since only the testis descends. A few examples of children in whom an incorrect diagnosis was made are as follows:

Case 1: (Fig. 1) This child was diagnosed at birth to be a male with perineal hypospadias and bilateral undescended testes by the obstetrician and Paediatrician. Fortunately a surgical consult was obtained. On rectal examination the surgeon was suspicious that this may be a patient with congenital adrenal hyperplasia (CAH) since he was able to express mucus from the "urethral" opening. He initiated the investigations that resulted in the correct diagnosis. Her CAH was easily controlled with appropriate medications and she was referred to us at 5 months age for surgical reconstruction.
Fig. 1. This girl with well controlled CAH was referred to us from Iran for surgical reconstruction at 5 months of age. At birth, she had been diagnosed as a male with perineal hypospadias and bilateral undescended testes and a surgical consult was obtained. The surgeon questioned the diagnosis and he initiated the investigations that resulted in the correct diagnosis.

Fig. 1a. The phallus had a stretched length of 3.5 cm. There appeared to be an empty bifid scrotum.

Fig. 1b. A solitary orifice was noted between the labioscrotal folds.


Case 2: (Fig. 2) A one-month old girl was referred for bilateral inguinal herniorrhaphy. On examination, in addition to bilateral inguinal hernias, she had palpable gonads in both labia. The external genitalia were completely normal for a female, however, the vagina was foreshortened upon examination with a cystoscope and no cervix was visible in the vaginal vault. The clinical diagnosis of Complete Androgen Insensitivity Syndrome (CAIS) was confirmed by a chromosomal pattern of 46XY. Fortunately the family was comfortable with continuing to rear the child as a girl since there was no clitoral enlargement at all. If there had been clitoral hypertrophy and/or if the family had wished to have her raised as a male serious social problems could have arisen from this misdiagnosis.

Case 3: (Fig. 3) This baby was labeled a male with hypospadias by the obstetrician. Endocrinologists were consulted and they agreed with the diagnosis. They obtained a pelvic ultrasound examination in which the radiologist did not visualize a uterus. We were consulted a week later to explain details of the hypospadias repair to the parents. We found the stretched phallic length to be 1.0 cm and a solitary perineal opening. A gonad was palpable in the left labioscrotal fold. We felt a distinct cigar shaped uterus on rectal examination and we expressed mucus from the perineal opening. Upon reviewing the pelvic ultrasound we found a classic neonatal uterus which the radiologist had missed as he was not aware.

Fig. 2. This girl was referred for bilateral inguinal herniorrhaphy. We palpated gonads in both labioscrotal folds and questioned the diagnosis. Studies confirmed a chromosomal pattern of 46XY.

Fig. 2a. She had prominent labia with palpable gonads on both sides.

Fig. 2b. She had normal female external genitalia. On Vaginoscopy the vagina was foreshortened and no cervix was visible.

Fig. 2c. Normal testes with well-defined gubernacula were found in both groins upon exploration. The arrow points to the skin puckering at the site of attachment of the left gubernaculum.

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Fig. 3. Transverse section of the pelvic ultrasound examination of the patient. The infantile uterus is the round structure marked by the three white arrows. The full bladder is labeled in the upper part of the illustration.


of the shape of an infant's uterus. The presence of Mullerian remnants excluded the diagnosis of 46XY DSD and asymmetry in gonadal descent suggested a working diagnosis of either ovotesticular DSD or MGD. The karyotype turned out to be a 45X/46XY mosaic. At laparoscopy, with a diagnosis of MGD, we found a uterus, left testis with vas deferens and right streak gonad. The gonads were removed due to a high risk of gonadoblastoma (25%). In this situation the child was given a male name before we were consulted and we were now faced with the difficult task of explaining a totally different opinion to the family. Fortunately having had prior experience with intersex in the family they understood the situation and they changed the sex of rearing to female. Then they had the difficult task of explaining the change in sex of the baby to family and friends.

The point is that even though assignment of the sex of rearing is a social emergency it must never be done without complete physical and laboratory evaluation of the child, careful thought to the nature and natural history of the underlying disease process and discussion with the family, psychologist and endocrinologist. Other issues that pertain to assignment of the sex of rearing will be discussed later. In case of uncertainty, it is better to delay assignment than to have to change the sex after the family has announced it to relatives and friends.

Inappropriate Sex Assignment

Until a short while ago it was believed that the sex of rearing from an early age superseded genetic sex. The importance of the androgen imprint on the brain was not known at the time.[1] Furthermore, until the early 1980s, our techniques for reconstructing males were relatively limited. As a result, some genetic males were raised and reconstructed as females. Whereas most of these children did very well, some became extremely unhappy. These patients have started a campaign that no genital reconstructive surgery should be done until the patient is old enough to consent for it. There is no evidence at present that males who have an artificially constructed phallus either because they have a miniscule phallus due to Partial Androgen Insensitivity Syndrome (PAIS) or no phallus because of CAIS will be happier as males than as females once they grow up. In addition, delaying reconstruction until the patient is an adult would mean that he would be subjected to scrutiny and possibly ridicule while undressed or even when he is unable to void standing up during his school years. We have previously reported on one of our patients with PAIS.[1] The child had a borderline phallus at birth. Today this patient would have been raised and reconstructed as a male. At that time, however, after discussion with the parents the child was reconstructed and raised as a girl. As a teenager she was an extremely unhappy lesbian, who would rebel by not taking the prescribed estrogens regularly. There is no way to predict which child will or will not take to sex reassignment hence it is probably safest to maintain the genetic sex as the sex of rearing whenever possible and to reconstruct genitalia appropriately. This course of action may still produce a patient who is unhappy with the appearance and function of his/her genitalia but at least we would not be adding to this unfortunate situation. Long-term evaluation will tell us whether this course of action is the better choice.

Insufficient or Incorrect Medical Management

Physicians, parents or even the patients may cause this problem. Physicians sometimes forget to increase the dose of steroids commensurate with growth of the child. Girls with
CAH are a prime example. They start to masculinize and become hirsute if dosages are not increased as they grow. Sometimes physicians make choices based upon their personal biases as in the case of a 46XY DSD patient in whom the administration of androgens was delayed until he was 17 years old, because he was slightly retarded mentally. Another was a CAIS patient, raised as a female after neonatal gonadectomy. In her case administration of estrogens was delayed because the physician felt she was not mature enough to handle puberty.

Parents are generally very good about administering medicines prescribed for their children, however, they too may slip up. One patient with CAH came to us at 7 years of age with recurrent clitoral hypertrophy, hirsutism and pubic hair growth of a full grown female (Fig. 4). The mother was aware of the diagnosis and she confessed that she knew that her daughter would require medicines all her life. She stopped giving the steroids at 5 years of age because the child was doing so well and looked "perfect". In another case the mother of a 17 year old CAIS patient who had bilateral gonadectomies as a neonate did not start administering estrogens as prescribed because she was concerned that the patient might become sexually active.

When the patients themselves are old enough to make decisions, they may miss doses or completely discontinue medicines. Teenagers with any chronic problem tend to forget their medicines from time to time. In addition, we have treated numerous patients with CAH who, when upset with their situation or with the family, rebel by discontinuing steroids (Fig. 5). We previously described a patient with PAIS who was raised as a female. She also refused to take estrogens from time to time when she was upset with life. We have also found this type of rebellious behavior in patients with CAIS, MGD and ovotesticular DSD. Patients who do not take their hormones appropriately after early gonadectomy develop an eunuchoid habitus (Fig. 6).

**Improper Reconstruction**

By far, the majority of complications occur in this category.

**Reconstruction of the Male**

Since each case is slightly different and numerous abnormalities coexist we believe that to plan the reconstruction properly and also to communicate adequately with other
This 46XY DSD patient had bilateral gonadectomies as an infant. She was not started on estrogens until 14 years of age when these photographs were taken. She was 5'10" tall.

**Fig. 6a.** Note the eunuchoid appearance

**Fig. 6b.** The patient lacks breast development and she has no axillary hair.

Physicians each of the following features should be evaluated and noted individually: 1) stretched penile length and presence of two corpora cavernosa, 2) shape and width of the glans penis, 3) location and size of the meatus, 4) location of the chordee (on the shaft, the glans or both), and its severity, 5) size and appearance (bifid or unified) of the scrotum and 5) amount of local skin available for reconstruction.

We feel it is best to carry out the reconstruction early so that any follow-up operations are completed by the time the child starts attending school. It is also preferable to carry out a one-stage reconstruction as far as possible. A common complication is persistent chordee. It either results from inadequate excision of fibrous tissue of the chordee or from construction of too short a neourethra. Regarding the former, it is essential to remove all the longitudinal fibrous bands on the ventral aspect of the corpora. An artificial erection helps confirm that the entire chordee has been excised. If local skin for reconstruction is lacking, administration of local or systemic testosterone for a short time seems to not only enlarge the phallus but it also causes growth of genital skin.

With regard to the neourethra, meatal stenosis, retraction, stricture, and urethrocrotaneous fistula are all well known. Meatal stenosis occurs when the neourethra is not sutured precisely to the glans or if it is placed in a tight glanular tunnel. The meatus retracts if the neourethra is too short. Since skin tends to retract after it has been dissected out, we mark the length and width of the flap at 1½ times the desired dimension. Thus, if we plan on a neourethra that will be 2 cm in length the skin flap is kept 3 cm long. Similarly, if the skin flap is not wide enough it strictures. When using urethral sounds, 1Fr size equals 1mm in circumference i.e. for a 10Fr neourethra, the skin flap has to be 10 mm wide after it has been dissected out. Accounting for shrinkage, we would make a 15 mm wide flap. Urethrocrotaneous fistulae occur if edges of the neourethra are not sutured precisely, dermis to dermis or if there is a distal obstruction in the neourethra or at the meatus. They occur at the proximal end of the suture line of the neourethra. Two out of three urethrocrotaneous fistulae heal spontaneously. If a urethrocrotaneous fistula does not heal, the urethra must be imaged and if a distal obstruction is found it has to be corrected prior to repair of the fistula to avoid its recurrence (Fig. 7). In the long-term hair and calculi can develop in the neourethra. This was particularly true when split thickness skin grafts were used in the construction of the neourethra. Bladder mucosal grafts tend to stenose at the meatus as bladder mucosa should not be exposed to air or allowed to dry. This problem can be avoided by anastomosing the graft to the glans in such a manner as to draw the glans in rather than have the mucosa pout outwards. Buccal mucosal grafts seem to be a better choice as they are more hardy and stable. Lately, tissue expanders have gained favor with some surgeons. They can be applied to the dorsum of the shaft of the penis or in the groin. Once the skin has expanded, pedicle flaps may be developed for reconstruction. Long-term results of this technique are awaited. There is a possibility that pedicle flaps from the groin would result in hair growth in the neourethra once the child reaches puberty.

**Fig. 7.** Oblique lateral view of voiding cystourethrogram of a boy with a urethrocrotaneous fistula (white arrow) after hypospadias repair. Note the stenosed distal neourethra.
Often the two halves of the scrotum have not migrated enough in these patients and they constitute what is often referred to as the "doughnut" scrotum. In such cases they should be reshaped by carrying out an inverted V to inverted Y-plasty in each hemi-scrotum (Fig. 8).

Category II-Enlarged clitoris with minimal posterior labial fusion. The urethral opening is visible at the anterior aspect of the UGS.

Category III-Enlarged clitoris with funnel shaped UGS. The urethra and vagina can only be visualized by looking into the UGS.

Category IV-Clitoris is significantly enlarged and appears to be a penoscrotal hypospadias because the high UGS opens at the base of the phallus.

Category V-Clitoris is enlarged even further and the high UGS opens just below the glans. The appearance is of a coronal hypospadias.

The optimal time to reconstruct female genitalia is generally believed to be in infancy. We do not agree with this since we have seen many more complications from vaginal reconstruction in infancy than with reconstruction in a 7-9 year old who is better able to cooperate with the parents and physicians.

Complications involve every component of female genitalia. In our series of 25 patients who presented with poor results of prior treatment, twenty two had an inadequate vagina. In 12 the vagina had stenosed after surgery. Another 9 patients with a narrow vaginal introitus had been treated unsuccessfully with dilations while the diagnosis of an inadequate introitus was missed in 1 patient. Thirteen patients had persistent clitoral hypertrophy while 3 had unsightly clitorectomies. Ten patients in the group also required reshaping of their scrotalized labia.

The flaccid clitoris of the adult female is about 2.5 cm in length and normally has a chordee because of its short frenulum. When the female is sexually excited, the clitoral corpora become turgid and elongate. However, because of the tight frenulum, the chordee becomes more pronounced and the clitoris is drawn towards the anterior edge of the vaginal opening where it is stimulated directly by the dorsum of the shaft of the penis during sexual intercourse and indirectly by traction on the frenulum with penile thrusting. However, there are no norms for the appropriate length of the clitoris in girls of various ages hence the decision to reduce the clitoris is made empirically. We consider two issues. First, the clitoris of the normal flaccid clitoris is not visible when the child's thighs are close together. Secondly, based upon our observations with normal clitorides in children we have established the following set of norms. The vaginal introitus is midway between the tip of the clitoris and the anterior edge of the anus and the glans clitoris is midway between the inferior edge of the pubic symphysis and the urethra. We believe that it is better to leave the clitoris too long rather than too short so that it may be stimulated during sexual activity. Therefore we do not reduce it unless the glans of the flaccid
clitoris is overtly visible between the thighs or it is approaching the urethral meatus. These criteria are valid for Prader's categories I, II, and III. In categories IV and V, it is difficult to measure these distances.

Over the years, numerous procedures have been devised to deal with the enlarged clitoris. Clitoridectomy is condemned since it eliminates the sensitive glans, thus is detrimental to sexual gratification of the female. Subcutaneous recession of the clitoris results in an unsightly pubic bulge when the clitoris is erect, hence we do not recommend the procedure. A clitoris that is recessed under the pubis buckles when it elongates and causes pain hence this procedure is also best avoided. The best approach is clitoral reduction (shortening of the corpora) with careful preservation of the dorsal neurovascular bundle, the glans and the frenular attachment of prepuce to the glans. In new cases this is relatively simple to do, with a "T" shaped incision on the dorsum of the clitoris. The long limb of the "T" runs along the dorsum of the clitoris and the short transverse limb is placed immediately proximal to the corona. However, in patients who had prior inadequate or inappropriate procedures on the clitoris, extreme care is required in identifying and preserving the neurovascular bundle since it may be displaced and adherent to the overlying skin. When redoing a clitoroplasty we approach the bundle by first making the horizontal incision. The skin flaps are raised laterally and dissected towards the midline since the bundle is relatively constant in the midline near the glans.

For reconstructive purposes, vaginal lesions are divided into two large groups: 1) Urogenital sinus (UGS) and 2) Absence or atresia of the vagina.

In patients with a UGS one must first determine the location of the confluence of the urinary tract with the vagina. Sinograms, in which radiographs are taken after instilling contrast in every perineal opening, and panendoscopy, where a cystoscope is used to visualize the anatomy, are essential for proper evaluation. In our experience low urogenital sinuses are undertreated and often are only dilated. The assumption that the posterior fold of skin and subcutaneous tissue will be pushed backwards during sexual activity is incorrect. In fact, the tissue is pushed forwards with penile thrusting, resulting in dyspareunia. We have treated patients who dilated the low UGS regularly for years without benefit. Incising the posterior flap and displacing it to the sides treats this lesion very effectively. Intermediate UGS requires a U-flap vaginoplasty, with a broad based, inverted U-shaped, thick flap the tip of which is laid into the apex of the posterior midline incision in the UGS. We have more experience in reconstructing high UGS with the pull-through procedure. It is essential in high UGS lesions to free the vagina circumferentially to advance it towards the perineum. In addition anterior and posterior thick flaps of perineal skin have to be raised to meet the vagina which may not reach all the way down to the perineum. Total urogenital mobilization is a relatively new procedure with good results to date but long-term results pertaining to urinary control, sexual function, maintenance of pregnancy and delivery of the baby are awaited.

The most common complication in intermediate and high UGS is the development of introital stenosis. Regular dilation is essential after reconstruction of these lesions. Unfortunately, this is difficult to achieve in the younger child. We found an unusual complication in a patient who came to us as a teenager after having a pull-through for a high UGS as an infant. The surgeon missed the midline and brought the vagina to one side of the perineum. The urethra of patients with intermediate UGS tends to enter the anterior aspect of the introitus of the reconstructed vagina, often mislabeled as "female hypospadias". This can result in irritation with sexual activity. On occasion vulvar tissues have to be tubularized from the original location of the urethra so the new meatus could be moved anteriorly outside the introitus (Fig. 9). A full thickness skin flap from a labium majus is rotated to cover the anterior meatus. It is critical to advance the repair to the new location of the urethra.

Fig. 9. This patient had an intermediate level UGS which was reconstructed with a U-flap vaginoplasty. Her urethra opened low in the anterior wall of the vagina. She complained of spraying of urine and dysuria after sexual intercourse hence her urethra was lengthened anteriorly by rolling vulvar tissues over a catheter. The white arrow points to the original location of the urethra while the black arrow demonstrates the new urinary meatus with a catheter in it. A skin flap has been raised from her left labium majus and the black outlined arrow indicates the direction in which the flap will be rotated to cover the neourethra.

neourethra. In patients with CAH, often the labia are very prominent and appear like a bifid scrotum. The problem is corrected by Y-V plasty in each labium whereby the redundant tissues are stretched caudally. This procedure can be incorporated into the vaginoplasty by using the long limb of the Y for the vertical limb of the inverted U.\(^2\)

Vaginal atresia may be complete or partial. Furthermore there could be a transverse septum at any level in the vagina or even a coronal septum. Septa are excised as required. Patients with foreshortened vagina and vaginal atresia require a neovagina. Over the years numerous tissues and techniques have been tried.\(^3\) We have constructed neovaginas from thick partial thickness skin grafts and colon.\(^6\) Skin graft neovaginas offer the benefit of not needing a laparotomy. However, the patient has a scar at the donor site (usually on the buttocks), loss of part or all of the graft is possible, daily dilation is essential until the patient is regularly sexually active and external lubrication is needed for sexual intercourse. Colovaginoplasty, on the other hand, provides an excellent vascularized pedicle graft usually from the sigmoid colon, the colon does not shrink if not used and it is well lubricated for sexual intercourse. Some patients consider the mucus secretion of the colon to be excessive. This problem is easily handled if the patient uses a tampon. The only technical complication in our cases was mild introital stenosis on occasion but it was easily dilated. Others have noted some other complications on long-term follow-up.\(^7\) The colon is a particularly versatile structure and it can be used in novel ways for complex anomalies.\(^8\)

**Inadequate Resolution of Psychological Issues**

It is now apparent that psychological issues must receive much greater attention than they received in the past. First we have to deal with parental concerns when the patient is an infant. They must be privy to all the information available so as to make an informed decision regarding the child's sex of rearing, general upbringing and nature and timing of reconstructive operations. Secondly they must be helped in avoiding accidental disclosure of the problem. If one or both parents find it difficult to accept that their child has a genital deformity, they must be counseled and receive support from other families with such children. In the past, in our practice and in referred cases, not enough attention was paid to psycho-social matters.

Once these children are old enough to understand that they have a chronic problem that will affect them for their entire life, they tend to rebel by not cooperating with various aspects of the management including refusal to take medicines appropriately. This self-destructive behavior constitutes a very serious issue since it hampers further treatment and may cause localized and generalized complications that require intensive therapy and reparative surgery.

Finally, the issue of the androgen imprint on the brain is very important. In genetic males with at least a borderline phallus this problem can be avoided by raising and reconstructing them as males. The question of CAIS patients is more complex. An artificial penis can be constructed. However, it does not have sexual sensation nor does it function normally. We do not know how well these children will do once they grow up. Patients with 46XX DSD have normal female internal genitalia hence they are best raised as females with appropriate reconstruction. However, the intrauterine exposure to androgens produces an imprint on their brains too. It affects their body image and also results in an increased incidence of homosexuality.\(^9\) At present, for 46XX DSD, we can only offer ongoing psychological counseling since it is not possible to reverse the androgen imprint on the brain.

**Conclusion**

Ambiguous genitalia or disorders of sex development are the result of numerous complex abnormalities that must be diagnosed correctly, their long-term effects have to be understood and appropriate genital reconstruction must be carried out only after complete evaluation. For some of their psychological issues we do not have answers at this time.

**References**

