Intersex

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Intersex)) Disorders of sex development

These may be diagnosed at birth with ambiguous or abnormal genitalia, but may also be seen at puberty.in girls who present with primary amenorrhoea or

increasing virilization. There has been a recent change in the terminology

used to refer to these conditions. Older terms, such as ‘hermaphrodite’ and ‘intersex’, are confusing to both the clinician and patients, and in addition can

be hurtful.So intersex was changed to the term of (Disorders of sex development)

Chromosomal abnormalities

Turner syndrome

If an embryo loses one of its sex chromosomes, then the total complement of chromosomes is 45. This is usually incompatible with life, except in the case of Turner syndrome which results from a complete or partial absence on one X chromosome .(45XO)

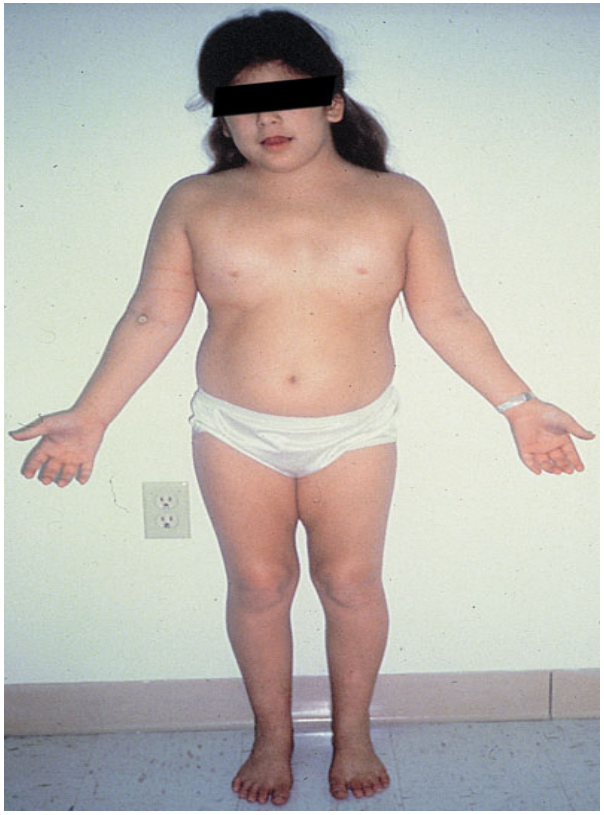
Turner syndrome is the most common chromosomal anomaly in females, occurring in 1 in 2500 live female births. Although there can be variation among affected women

most have typical clinical features including short stature, webbing of the neck and a wide carrying angle. Associated medical conditions include coarctation of the aorta, inflammatory bowel disease, sensorineural and conduction deafness, renal anomalies and endocrine dysfunction, such as autoimmune thyroid disease

In this condition, the ovary does not complete its normal development and only the stroma is present at birth. The gonads are called ‘streak gonads’ and .do not function to produce oestrogen or oocytes

Diagnosis is usually made at birth or in early childhood from the clinical appearance of the baby or due to short stature during childhood. However, in about 10 per cent of women, the diagnosis is not made until adolescence with delayed puberty. The ovaries do not produce oestrogen, so the normal physical changes of puberty cannot happen. In childhood, treatment is focused on growth, but in adolescence it focuses on induction of puberty. Pregnancy is possible, but ovum donation is usually required.

.Psychological input and support is important

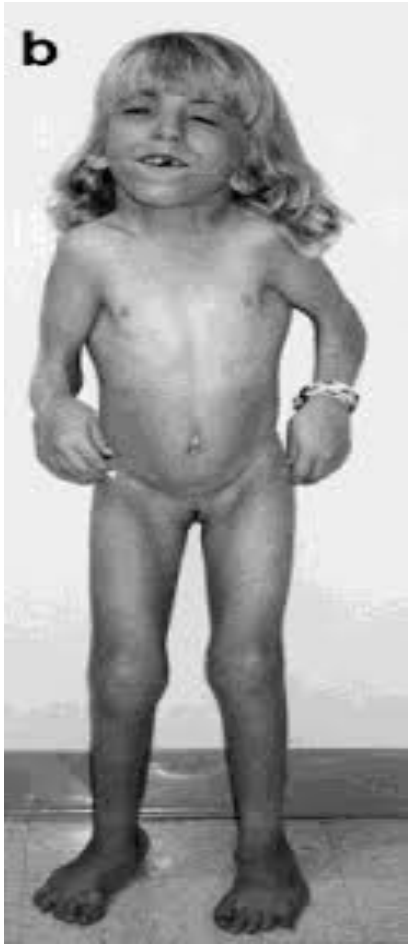


XY gonadal dysgenesis

In this situation, the gonads do not develop into a testis, despite the presence of an XY karyotype. In about 10 per cent of cases, this is due to an absent .SRY gene, but in most cases the cause is unknown

In complete gonadal dysgenesis (Swyer syndrome), the gonad remains as a streak gonad and does not produce any hormones. In the absence of AMH, the Mullerian structures do not regress and the uterus, vaginal and Fallopian tubes develop normally

Mixed gonadal dysgenesis is a more complex condition. The karyotype may be 46 XX, but mosaicism, e.g. XX/XY, is present in up to 20 per cent. In this situation, both functioning ovarian and testicular tissue can be present and if so this condition is known as ovotesticular DSD. The anatomical findings vary depending on the function of the gonads. For example, if the testes is functional, then the baby will virilize and have ambiguous or normal male genitalia. The Mullerian structures are usually absent on the side of the functioning testes, but a unicorcuate uterus may be present if there is an ovary or streak gonad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46XY DSD

Complete androgen insensitivity syndrome (CAIS) occurs in individuals where virilization of the external genitalia does not occur due to a partial or complete inability of the androgen receptor to respond to androgen stimulation. In the fetus with CAIS, testes form normally due to the action of the SRY gene. At the appropriate time, these testes secrete AMH leading to the regression of the Mullerian ducts. .Hence, CAIS women do not have a uterus

Testosterone is also produced at the appropriate time, however, due to the inability of the androgen receptor to respond, the external genitalia do not virilize and instead undergo female development. A female fetus is born with normal female external genitalia, an absent uterus and testes found at some point in their line of descent through the abdomen from the pelvis to the inguinal canal. During puberty, breast development will be normal, however, the effects of androgens are not seen, so pubic and axillary hair .growth will be minimal

Presentation is usually at puberty with primary amenorrhoea, although if the testes are in the inguinal canal they can cause a hernia in a younger girl. Once the diagnosis is made, initially management is psychological with full disclosure of the XY karyotype and the information that the patient will be infertile. Gonadectomy is recommended because of the small long-term risk of testicular malignancy, although this can be deferred until after puberty. Once the gonads are removed, long-term .hormone replacement therapy will be required

The vagina is usually shortened and treatment will be required to create a vagina suitable for penetrative intercourse. Vaginal dilation is the most effective method of improving vaginal length and entails the insertion of vaginal moulds of gradually increasing length and width for at least 30 minutes a day

Surgical vaginal reconstruction operations are reserved for those women that have failed a dilation treatment programme.
In cases of partial androgen insensitivity, the androgen receptor can respond to some extent with limited virilization. The child is usually diagnosed at birth with ambiguous .genitalia

Vaginal dilators

Alpha-reductase deficiency-5

In this condition, the fetus has an XY karytype and a normal functioning testes which produce both testosterone and AMH. However, the fetus is unable to convert testosterone to dihydrotestosterone in the .peripheral tissues and so cannot virilize normally

Presentation is usually with ambiguous genitalia at birth, but can also be with increasing virilization at puberty of a female child due to the large increase in circulating testosterone with the onset of puberty. In the Western world, the child is usually assigned to a female sex of rearing, but there have been descriptions of a few communities where transition from a female to male gender at puberty is accepted

Congenital adrenal hyperplasia

This condition leads to virilization of a female fetus. It is due to an enzyme deficiency in the corticosteroid production pathway in the adrenal gland with over 90 per cent being a deficiency in 21-hydroxylase, which converts progesterone to deoxycorticosterone, and 17-hydroxyprogesterone (17-OHP) to deoxycortisol. The reduced levels of cortisol being produced drive the negative feedback loop, resulting in hyperplasia of the adrenal glands and increased levels of progesterone production. This leads to an excess of androgen precursors and then to elevated testosterone production. Raised androgen levels in a female fetus will lead to virilization of the eternal genitalia. The clitoris is enlarged and the labia are fused and scrotal in appearance. The upper vagina joins the urethra and opens as one common channel onto the perineum.

In addition, two thirds of children with 21-OH CAH will have a ‘salt-losing’ variety, which also affects the ability to produce aldosterone. This represents a lifethreatening situation, and those children who are salt-losing often become dangerously unwell within a few days of birth. Affected individuals require lifelong steroid replacement, such as hydrocortisone – along with fludrocortisone for salt losers. Once the infant is well and stabilized on their steroid regime, surgical treatment of the genitalia is considered

Traditionally, all female infants with CAH underwent feminizing genital surgery within the first year of life. This management is now controversial as adult patients with CAH are very dissatisfied with the outcome of their surgery and argue that surgery should have been deferred until they were old enough to have a choice. Surgery certainly leaves scarring and may reduce sexual sensitivity, but the alternative of leaving the genitalia virilized throughout childhood can be difficult for parents to consider. At present, cases are managed individually by a multidisciplinary team involving surgeons, endocrinologists and psychologists.

Mullerian anomalies

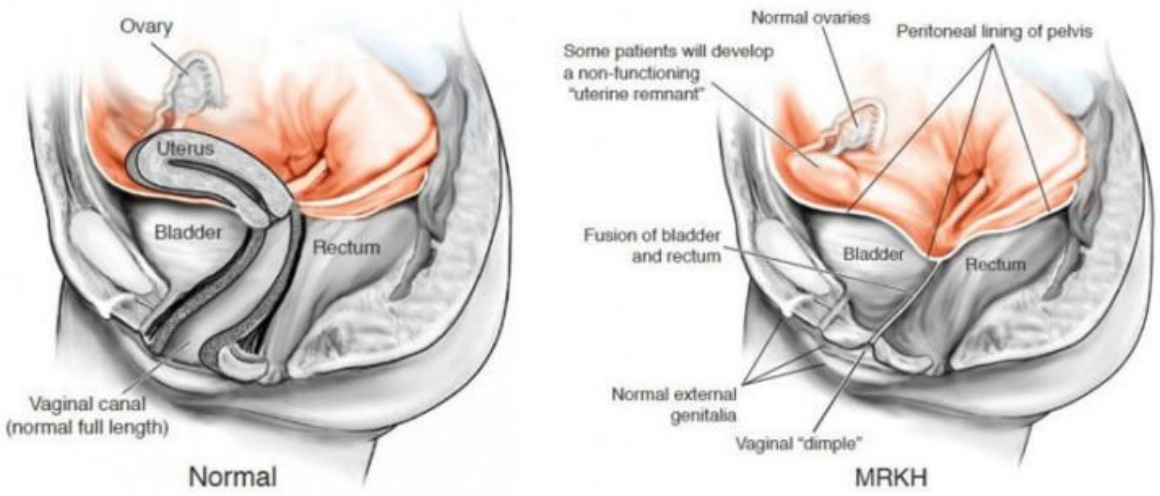
These are common, occurring in up to 6 per cent of the female population, and may be asymptomatic. The aetiology is unknown, .although associated renal anomalies are present in up to 30 per cent

Mullerian agenesis

In approximately 1 in 5000 to 1 in 40 000 girls, the Mullerian system does not develop resulting in an absent or rudimentary uterus .and upper vagina

This condition is known as Rokitansky syndrome or Mayer–Rokitansky–Kuster–Hauser (MRKH) syndrome. The ovaries function normally and so the most common presentation is with primary amenorrhoea in the presence of otherwise normal pubertal development. The aetiology of this condition is not known although possible culprits include environmental, genetic, hormonal or receptor factors

On examination, the vagina will be blind ending and is likely to be shortened in length. An ultrasound scan will confirm the presence of ovaries, but no functioning uterus will be present. Treatment options focus on psychological support and on the creation of a vagina comfortable for penetrative intercourse, as described above for CAIS. There is currently no treatment available to transplant a uterus in humans, although there is extensive ongoing research being undertaken in this area. Women with MRKH syndrome may have their own genetic children, using ovum retrieval and assisted conception techniques, and a surrogate mother


Ovary
Uterus
Bladder
Rectum
Vaginal canal
(normal full length)
Normal
Normal ovaries
Peritoneal lining of pelvis
Some patients will develop
a non-functioning
"uterine remnant"
Fusion of bladder
and rectum
Bladder
Rectum
Normal external
genitalia
Vaginal "dimple"
MRKH