

Androgen Insensitivity Syndrome (AIS)

Androgen Insensitivity Syndrome (AIS) is one of a number of biological intersex conditions. Intersex is a variant from the usual embryological development of the reproductive tract, often determined by a known genetic mutation. It is a condition that affects the development of the reproductive and genital organs. Before going through AIS in depth, it will be advisable to know the intersex conditions first.

What is Intersex?

The XX/XY sex-determination system is the most familiar sex-determination systems, as it is found in human beings, most other mammals, as well as some insects. In the XY sex-determination system, females have two of the same kind of sex chromosome (XX), while males have two distinct sex chromosomes (XY). The XY sex chromosomes are different in shape and size from each other unlike the [autosomes](#), and are termed [allosomes](#).

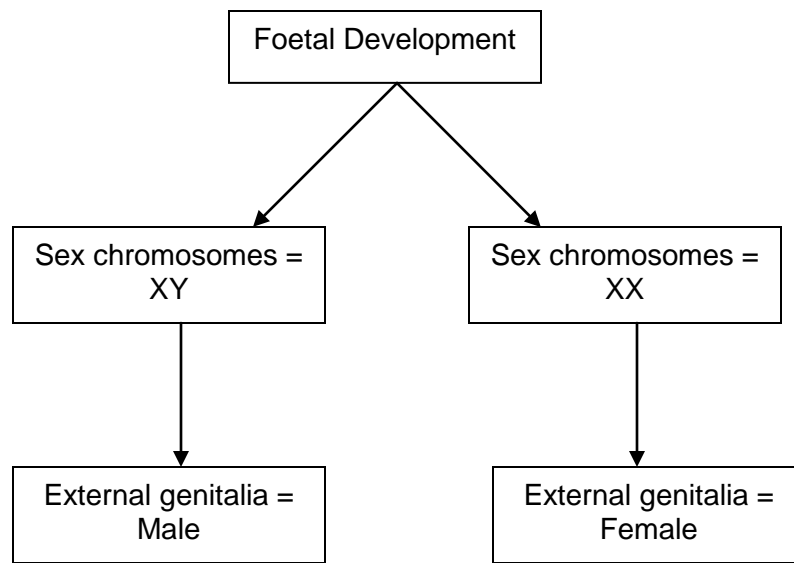
The usual pattern of human foetal development results in a 3-part alignment, as follows:

Either:

- 1) sex chromosomes = XY, leading to
- 2) gonads = testes, leading to
- 3) external genitalia = male

or:

- 1) sex chromosomes = XX, leading to
- 2) gonads = ovaries, leading to
- 3) external genitalia = female



The term 'intersex' refers to the elements of this entire alignment (the sex chromosomes, the gonads and the genitalia) and not just to the appearance of the external genitalia. A patient with the complete form of AIS (CAIS) or with Swyers Syndrome (XY gonadal dysgenesis), will always appear female externally (no ambiguity) but she is still intersexed, because she has XY chromosomes and internal testes (testicular streak gonads in the case of Swyers) that are at odds with her external femaleness.

The Truth Behind Eunuch Intersex

A hermaphrodite, is a purely mythical creature from ancient literature, one that supposedly has a complete working set of both male and female internal and external organs (such that the individual can, in theory, impregnate itself). This is not humanly possible. Unfortunately medicine took over this literary term in the days before genetics was understood and employed it as a medical term, to refer to these individuals who have both ovarian and testicular tissue internally (an ovo-testis) and who, as a result, can have ambiguous external genitalia.

Introduction to AIS

Male foetuses usually have a Y sex chromosome which initiates the formation of testes (and the suppression of female internal organ development) during gestation. Testes are the site of production of masculinizing hormones (specially androgens) in large quantities.

Both male and female foetuses usually have at least one X sex chromosome, which contains a gene that gives their body tissues the capacity to recognise and react to androgens. At puberty girls react to the relatively small quantity of androgens (that come mainly from their adrenal glands) by developing pubic and underarm hair and darkish pigmentation around the nipples.

People with AIS have a functioning Y sex chromosome (and therefore no female internal organs) but an abnormality on the X sex chromosome that renders the body completely or partially incapable of recognising the androgens produced. In the case of

complete androgen insensitivity (CAIS), the external genital development takes a female form. In the case of partial insensitivity (PAIS), the external genital appearance may lie anywhere along the spectrum from male to female. Other related conditions, resulting from changes on different chromosomes, also disrupt the normal pathway of androgen action, resulting again in a feminized phenotype (body form).

People with these 'XY conditions' may identify as female, intergendered or male.

AIS: Complete and Partial

As mentioned there are two forms of the condition: Complete AIS (CAIS) where the tissues are completely insensitive to androgens and Partial AIS (PAIS) where the tissues are partially sensitive to varying degrees. The condition is actually represented by a spectrum, with CAIS being a single entity at one end of a range of various PAIS manifestations.

Drs. Charmian Quigley and Frank French (The Laboratories for Reproductive Biology, The University of North Carolina at Chapel Hill, North Carolina 27599-7500, USA) proposed a grading system for the phenotypic features (external appearance) in AIS, modelled on the Prader classification for Congenital Adrenal Hyperplasia (CAH). The scale runs from AIS Grade 1 to Grade 7 with increasing severity of androgen resistance - and hence decreasing masculinization with increasing feminization.

The most (90%) girls have completely normal female type external genitalia, but they lack a uterus or upper vagina. This is known as Complete AIS (CAIS, technically AIS Grades 7 & 6). The remaining girls have Partial AIS (PAIS), their outward genital appearance usually lying anywhere from almost completely female (AIS Grade 5, 4) through to almost completely male (Grade 3 to 1).

At the CAIS end of the spectrum the outward appearance is completely female (AIS Grades 6/7) and the sex of rearing is invariably female. In PAIS the outward genital appearance can lie anywhere from being almost completely female (Grade 5), through mixed male/female, to completely male (Grade 1); it has been suggested that slight androgen insensitivity might contribute to infertility in some otherwise normal men. Some babies with PAIS may be raised as males but many are re-assigned as female.

Grades of PAIS

The term 'severe PAIS' is sometimes used to refer to Grades 5 and 6, to distinguish them from the lower grades of PAIS. In AIS Grades 5 and 4, the clitoris is enlarged. In Grade 5, there may be partial fusion of the labia majora (outer vaginal lips), in which the

posterior (back) portion of the labia form a web of tissue across the back part of the vaginal outlet. In Grade 4, this fusion extends further forward, covering both the vaginal opening and the true urethral opening. The cavity formed by the fused labia, through which urine exits, is called a urogenital sinus.

The labial fusion can be surgically divided, making the vaginal opening accessible for pressure dilation (a non-surgical way of lengthening the vagina). This division is a relatively minor operation and is unlikely to adversely affect erotic sensitivity but it should be performed by a surgeon familiar with this type of surgery. Vaginal dilation can be successful in Grade 4 AIS and should always be attempted before surgical vaginoplasty.

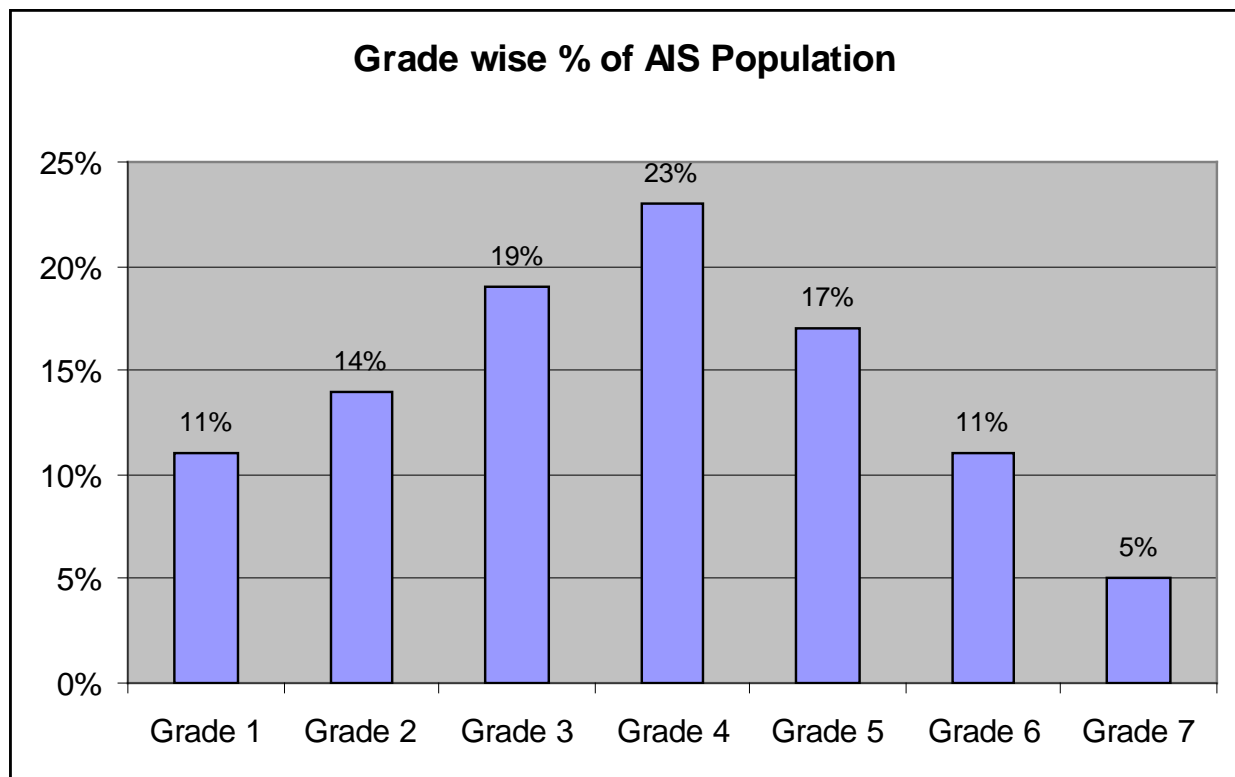
In Grade 3 and the more masculinized form of Grade 4, the labia are completely fused, so that the urethral opening is at the base of the clitoris/penis. The fused labia may have a rugose or wrinkled appearance and form a bifid or double, scrotum. The fusion is then more properly called 'labio-scrotal fusion'. The phallus has the appearance of a large clitoris or a small, bent, penis, bound down in structures called chordee. The chordee is formed from the same tissues that form the labia minora in the female and the frenulum of the penis and the tissues surrounding the urethra (corpus spongiosum) on the underside of the penis in the male. It is not true that the presence of chordee makes erections painful.

In Grade 2, the genital appearance is that of a male with hypospadias, that is, with a urethral opening located somewhere on the underside of the penis. There may be an open gutter running from the urethral opening to the glans of the penis.

Note: Hypospadias is not in itself an intersex condition but is a congenital condition of the penis which is fairly common, affecting approximately one in every 200 male births. It can be present in some cases of intersex (e.g. PAIS Grades 2 and 3). The urethra (the tube through which urine is expelled) fails to grow right through to the tip of the penis; instead, it opens on the underside, somewhere further back than is usual. In some

cases, the opening may be at the base of the penis or back on the scrotum and the penis might be curved downward.

Grade 1	PAIS	Male genitals, infertility
Grade 2	PAIS	Male genitals but mildly 'under-masculinized', isolated hypospadias
Grade 3	PAIS	Predominantly male genitals but more severely 'under-masculinized' (perineal hypospadias, small penis, cryptorchidism i.e. undescended testes and/or bifid scrotum)
Grade 4	PAIS	Ambiguous genitals, severely 'under-masculinized' (phallic structure that is indeterminate between a penis and a clitoris)
Grade 5	PAIS	Essentially female genitals (including separate urethral and vaginal orifices, mild clitoromegaly i.e. enlarged clitoris)
Grade 6	PAIS	Female genitals with pubic/underarm hair
Grade 7	CAIS	Female genitals with little or no pubic/underarm hair



Before puberty, individuals with Grade 6 or 7 are indistinguishable.

Genetics – Normal (non-AIS) Situation

In human somatic (body) cells there are normally 46 chromosomes made up of 23 pairs. 44 of the 46 are called autosomes because they are not thought to determine gender. The other two are called sex chromosomes. Non-AIS males have a relatively large X and a small Y sex chromosome and normal females have two X sex chromosomes.

When the generative cells are formed in the body of the adult, these sex chromosomes become separated, so that a sperm carries either a single X or a single Y chromosome, whilst every egg carries a single X chromosome. At conception the new embryo will be XX or XY, according to whether the egg, which is always X, was fertilized by an X-bearing sperm or by a Y-bearing sperm. Thus the sperm controls the genetic sex of the child.

Foetal Development – Normal (non-AIS) Situation

Although the sex of the embryo is determined at the time of conception, anatomical differences don't show until approximately two months later. In this 'indifferent stage' every foetus has the primitive structure necessary for either a male or a female system: there are both Wolffian ducts and Mullerian ducts.

Gonad is the term given to the undifferentiated organ that will later become either a testis or an ovary. Testes develop earlier than ovaries. In an XY foetus, the gonads develop into testes. The testes then cause the Wolffian ducts to develop into the rest of the internal male system and the Mullerian ducts to be suppressed. In an XX foetus, the gonads develop into ovaries, the Mullerian ducts then form the rest of the female internal system and the Wolffian ducts are suppressed.

It is important to understand not only is there a single primitive structure in the indifferent stage from which both, either male or the female organs develop but that, each reproductive organ in either sex has a counterpart in the opposite sex. For example, the penis of the male and the much smaller clitoris of the female both come from the embryonic genital tubercle or phallus. Men have a vestigial uterus, the utriculus

masculus in the prostate and women have a homologue prostate in the glands at the lower end of the urethra.

Foetal Development – Abnormal AIS Situation

In the case of an AIS foetus, a Y-bearing sperm fertilizes the egg (which is always X) and produces an XY embryo. In the early stage of foetal life differentiation is as a male, with testes and the Mullerian ducts regressing. The Mullerian ducts would have formed the internal female organs in an XX girl. Once the testes are formed, they start to produce testosterone, which would normally cause the masculinization of the body.



Until about 10 weeks of gestational age, male and female embryos appear identical in external anatomy. The same structures then begin to differentiate as male under the influence of testosterone or as female if the influence of testosterone is absent. In the presence of intermediate amounts of androgens or in a condition of partial sensitivity to androgens, the external genitalia will develop in an in-between way. In PAIS, the external genitalia can therefore be ambiguous, that is, intermediate in structure between male and female. Note that the structure of ambiguous external genitalia can be the same, whether the genetic sex and the sex of the gonads is male or female. The structure of the external genitalia does not provide a way to determine whether the condition is PAIS or some other intersex condition.

Masculinization is an active process; it needs the positive or active intervention of the male hormones in order to take place. If these male hormones are either absent or the tissues do not respond to them (as happens to differing degrees in the various forms of AIS), then the passive tendency is for the external genitals to differentiate into female external organs which, in the complete form of AIS, are indistinguishable from those of normal girls. This female physical development is not due to the presence and influence of oestrogens but to the ineffectiveness of androgens. In other words, the inherent trend for any foetus is to develop female external genitals and general body form, in the absence of the masculinizing effects of male hormones.

Unfortunately, however, by the time the androgen insensitivity in AIS becomes evident, the internal reproductive organs have already progressed partially down the male route and the Mullerian Inhibitory Factor (MIF) from the testes has already begun its work of destroying the primitive female internal organs. The testes remain in a 'frozen', i.e. partially-developed male state and the development of the internal female organs cannot be reactivated.

The following considers the Complete form of AIS (CAIS).

The condition was originally assigned the name Testicular Feminization Syndrome (TFS) and is now replaced by the more accurate and much less stigmatizing term Androgen Insensitivity Syndrome (AIS). The physical manifestation of the condition are as follows:

- Female body shape
- Large breasts with juvenile nipples
- Absent/scanty axillary and pubic hair
- No temporal hair recession (balding)
- Female external genitalia with small labia
- Blind-ending vagina
- Absent or rudimentary internal genitalia
- Gonads consistent histologically with cryptorchid testes
- Hyperplasia of interstitial cells: adenoma
- Testes produce androgen and oestrogen

- Increased gonadotrophins.

Even in CAIS there will be no ovaries, Fallopian tubes or uterus; and the vagina will be blind-ending and possibly short or absent. Female pubertal development occurs but there will be no menstruation and no possibility of conceiving/bearing children (although genetic advances in infertility treatment are occurring quite rapidly).

Some girls with AIS may develop some dark, coarse pubic/underarm hair (AIS Grade 6) but usually this does not develop (Grade 7) because its growth is dependent on the effects of androgens. The nipples usually remain under-developed and pale in colour. The vagina may need to be lengthened or constructed before sexual intercourse by surgical means (see Vaginal Hypoplasia on page no. _____).

The undescended testes can result in an inguinal hernia in infancy and this is when AIS may be diagnosed in an apparently female child (approx. 50% of cases). Otherwise CAIS may not be discovered until puberty when there is a failure to menstruate (approx. 50% of cases). Failure to menstruate is known as primary amenorrhoea.

Pubic and Underarm (Axillary) Hair in AIS

Often the pubic hair in individuals with CAIS is reported as 'scanty' or 'sparse' and it is unclear whether the hair that is present is anything more than the vellus down (which is not androgen-dependent) similar to that found elsewhere on the body in both sexes, at all ages. True sexual hair - the longer, coarser, darker terminal hair characteristic of adult pubic and axillary regions - results from androgenic stimulation of hair follicles. The term pubic hair should therefore be confined to hair that is truly androgenic in nature, however sparse or abundant and its distribution should be described in terms of Tanner staging.

Some individuals, considered in infancy to have the complete form of AIS, develop sexual hair at puberty, sometimes of the density and distribution seen in the normal postpubertal, 46XX, female. The presence of true pubic hair, even in an AIS individual with an entirely female phenotype, must be regarded as evidence for some degree of

androgen responsiveness and that such individuals are considered to be having a severe partial form of AIS (Grade 6) rather than CAIS (Grade 7).

Changes at Puberty

Body Changes

Pubic and axillary hair growth is dependent on androgens. Even if the testes are still in place at puberty, pubic and axillary hair growth is likely to be sparse or absent.

Although androgens are often called "male hormones" and oestrogens are often called "female hormones," both types of hormones are present in males and females, just in varying in ratio. In normal males the body produces androgens and a smaller amount of oestrogens. In fact, the richest natural source of oestrone (one type of oestrogen) is the testis of the stallion. Similarly, normal females produce male as well as female hormones. In AIS the testicular oestrogen is secreted in a non-cyclical manner and not cyclically as in the menstruating female. Girls with AIS are particularly sensitive to oestrogens because of lack of the counter-effect of androgens.

Sensitivity to Oestrogens

In AIS, although the body is insensitive to androgens, it is very responsive to oestrogens and is affected by the small amount of oestradiol (an oestrogen) produced by the testes, by the oestrone produced from testosterone in fat tissue or the oestrogen replacement therapy given in the case where the testes have been removed.

This means that the body not only fails to develop masculinity but develops even further in a feminine direction, causing the body appearance to perfectly resemble an XX female, with female breast development. That may be the reason the older literature sometimes states that girls with AIS are often tall, that the body form is "voluptuously female", i.e. with very adequate breast development and that the skin maintains a good condition, not being prone to acne (which is linked to the effects of male hormones). However, since there is no uterus and no ovaries, there is no possibility of menstruation.

Although a vagina of sorts may be present, as mentioned earlier, it is usually no more than a short blind pocket and may require lengthening if intercourse is to be possible.

Growth - General

It is often stated that girls with AIS are taller than average. Contrary to this belief individuals with CAIS are phenotypic females 'with normal female appearance' and that their growth in stature and body proportions are normal, but there are some observations indicating that they might be taller than normal females. AIS girls tend to have a masculine skeleton and that the size of their teeth is closer to that of men than of women and they have elongated limbs and large hands and feet. An average height of about 157 cm is observed, which is slightly below normal for men but higher than that of women.

Some of these observations, however, might have been made at a time when the practice of early gonadectomy and HRT was not so common and thus did not present a possible externally-applied growth regulating factor!

Growth - Role of Oestrogens

Normal male pubertal growth spurt can be quite satisfactorily explained by the combined action of testosterone and growth hormone but that the mechanisms involved in the female growth spurt are not completely understood. Oestrogens had formerly been considered of minor importance and in the growth of girls more influence had been attributed to androgens from the adrenal glands. Their studies suggest however that in normal girls the pubertal growth spurt results from the effects of oestrogens rather than adrenal androgens. They conclude that in AIS the following changes take place:

- a spontaneous pubertal growth spurt takes place,
- the spurt velocity is equivalent to that in normal girls,
- it starts at an appropriate chronological age for girls (i.e. earlier than in normal boys) but
- bone maturation (i.e. closure of the long bones and hence mature height) corresponds to that of normal boys rather than normal girls.

Presumably these observations were in the absence of any HRT and therefore in spite of plasma oestrogen concentrations that would tend to be lower (due to lack of ovarian oestrogens) than in normal girls of the same age. They suggest that girls with AIS are particularly sensitive to oestrogens (as evidenced also by their good breast development) because of lack of the counter-effect of androgens.

Growth - Role of Y Chromosome

Some researchers in the field have suggested that genes on the Y chromosome have an effect on growth, independent of hormonal changes, as shown by increased growth in boys with an extra Y chromosome. In AIS "the XY karyotype (chromosomes) will result in excessive final height in relation to the female phenotype (body form)". The body shape (having accounted for size differences) of 46 XY females does not deviate much from that of normal females but that 46 XY females tend to be larger in all body measurements, although with a tendency to a slimmer body. The mean height (171.5 cm) of the 46 XY females was 10.2 cm higher than that of the normal females but was 4.9 cm lower than that of a sample of 40 normal males. They conclude that the Y chromosome has a direct influence on growth but that the greater height in normal males may indicate that an additive or inductive action of androgens is also necessary for the completion of body growth in normal males. They suggest that the body shape in 46 XY females is under the control of oestrogens and is not affected by the Y chromosome.