

# Androgen Insensitivity Syndrome: Differences of Sex Development

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Longevity  
HDE 117 or ENT 117  
UC Davis, Fall 2022

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## SUMMARY

The development of biological sex is a complex process involving the interaction of chromosomes, gonads, and hormones. Within these processes, differences/disorders of sex development can occur, which can result in an individual's chromosomes not aligning with their external/internal genitalia and/or gonads. One of these disorders is androgen insensitivity syndrome, an XY disorder of sex development that occurs during fetal development where the androgens required to develop the male internal and external genitalia goes undetected or partially undetected, resulting in an individual having XY sex chromosomes and female, ambiguous, or male external genitalia, depending on the severity of androgen insensitivity. This condition is not always identified at birth, but individuals with this condition are expected to have a normal lifespan. At puberty, adolescence with AIS may experience reduced pubic and axillary hair as well as varying levels of breast development. Severe forms of AIS can result in bone density issues and infertility. Treatments for androgen insensitivity syndrome include hormone replacement therapy, reconstructive and/or cosmetic surgery. Stigma presents an issue to psychological wellbeing in individuals with AIS, and the condition is associated with increased psychological morbidity. Certain non-essential cosmetic surgeries or genital normalization surgeries are controversial as the benefit may not outweigh the risk factors. Lack of clear communication within healthcare professionals can lead to a lack of compliance with treatment.

## INTRODUCTION

Sex assigned at birth is the label (male or female) given to a newborn by a medical professional that is generally based on the appearance of an infant's external genitalia alone. However, biological sex is more complex than this; hormones, chromosomes, and internal genitalia also play a factor. Biological sex can be categorized into three categories: genetic/genotypic sex (sex chromosomes such as XX, XY), gonadal sex (testes/ovaries), and phenotypic sex (external genitalia). Additionally, gender or gender identity can be defined as a person's perception of their sex (man, woman, etc.). While sex assignment is normally straightforward, this is not always the case. When a newborn has a difference/disorder of sex development (DSD), their "chromosomal, gonadal, or anatomic sex is atypical" (Walia et al., 2018; p364). These are also referred to as intersex conditions, as the distinction between male and female cannot always be made (Purves et al. 2001) (Planned Parenthood). Androgen insensitivity syndrome (AIS) is an XY DSD that occurs when an individual has XY sex chromosomes, but a female phenotype as the result of an insensitivity to androgens during fetal development (Agnethe et al., 2018).

## FETAL SEXUAL DIFFERENTIATION

Sex development begins as early as fertilization, as this is when the sex chromosomes of an embryo are determined. Until the 6<sup>th</sup> week of development, XX and XY embryos have sexually indifferent gonads and genital ducts (precursors to internal genitalia). The gonads are the first to differentiate into either testes or ovaries based on their respective chromosomes. For embryos with AIS, this process is typical as they possess functional XY chromosomes, meaning that they will develop testes. After gonadal sex is determined, the genital ducts will develop down a male or female path determined by hormones produced by the gonads. Both XX and XY embryos have two pairs of genital ducts that develop on the mesonephric kidneys (prototype kidneys). The pair of genital ducts are referred to as the Wolffian ducts and the Mullerian ducts. The Wolffian ducts will later develop into the male internal genitalia (vas deferens, epididymis, prostate, and seminal vesicle) and the Mullerian ducts will develop into the female internal genitalia (uterus, cervix, fallopian tubes, and upper vagina) [see figure 1]. XY embryos with AIS will have a complete or incomplete lack of Wolffian duct development, resulting in absent or impaired male internal genitalia (P. A. et al., 2022).

Figure 1. Sex differentiation of internal genitalia (Source: Goodman, 2009).

### Male

In the 7<sup>th</sup> week of development, if there is a functional SRY gene on the Y chromosome, then testes will develop. The SRY gene will then encode TDF protein and then the TDF protein will then activate the SOX9 and SF1 proteins, which will promote

the differentiation of cells in the undifferentiated gonads into Sertoli cells. The differentiation in these bipotent cells will lead to the development of primordial testes. The SOX9 and SF1 proteins will regulate AMH produced by the Sertoli cells and will prompt the regression of the Mullerian ducts. The virilization (masculinization of external characteristics) process of XY embryos that typically begins between the 8th and 14th week of development is dependent on the communication between androgens and androgen receptors (AR). Due to an insensitivity to androgens, XY fetuses with AIS do not undergo this virilization process, depending on the level of AR insensitivity (Ovidiu et al., 2022) (Sobel et al., 2004).

Androgens are set of sex hormones that both males and females produce, however androgens are especially important for developing a typical male phenotype (Cleveland Clinic 2021). Typical male sex differentiation as well as secondary sex characteristics are both due to androgens, the most important two being testosterone and 5 $\alpha$ -dihydrotestosterone (DHT) (Brinkmann, 2001). Testosterone is responsible for the development and differentiation of Wolffian ducts and DHT produced by the Leydig cells mediates the development of a male phenotype as well as the development of the prostate (Radmayr et al., 2009) [see figure 2].

Figure 2. Hormonal regulation of sex differentiation (Source: Rey et al., 2020).

### Female

Unlike the Wolffian ducts, the Mullerian ducts develop from a lack of hormone production. If there is no anti-Mullerian hormone (AMH) or testosterone produced by the gonads, then the Mullerian system will develop, and the Wolffian ducts will regress. The case for female external genitalia is a similar process, if there is a lack of androgen production, or in the case of AIS androgen detection, then a female phenotype will develop [see figure 3] (Rey et al., 2020) (Willson and Bordoni, 2022).

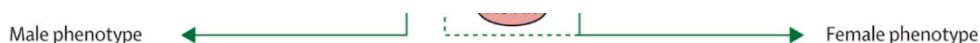


Figure 3. Pathway of fetal sex development (Source: Hughs et al., 2012).

## ANDROGEN INSENSITIVITY SYNDROME

AIS is a recessive genetic syndrome that is inherited on the X chromosome as the result of an AR mutation. While AIS traits and symptoms can vary based on androgen receptor sensitivity, AIS can be classified into three categories: complete androgen insensitivity syndrome (CAIS), partial androgen insensitivity syndrome (PAIS), and mild androgen insensitivity syndrome (MAIS). These categories are based on phenotypic sex; CAIS presenting a female phenotype, PAIS presenting an ambiguous phenotype, and MAIS presenting a male phenotype [see figure 4].

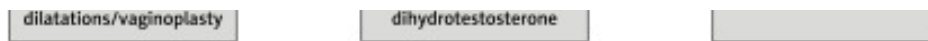


Figure 4. Diagnostic and treatment pathways for AIS (Source: Ovidiu et al., 2022).

The diagnostic process for this syndrome generally includes genetic and hormone testing, although in the case of CAIS, family history may also be examined. Treatment options for AIS can range from hormone replacement therapy to cosmetic and non-cosmetic surgery (Ovidiu et al., 2022).

### Characteristics and Diagnosis

Complete androgen insensitivity (CAIS) is marked by a complete insensitivity to androgens, meaning that there is little to no virilization of the external genitalia. As a result, infants with CAIS are almost always assigned female at birth. Additionally, people with CAIS normally have a female gender identify. Due to their female phenotype, CAIS generally goes undiagnosed until puberty. Although, in rare circumstances, when girls with CAIS have their testes located in their labia they can experience labia swelling due to the testes causing a hernia, which can point to a CAIS diagnosis. The first typical indicator that a child has CAIS is primary amenorrhea, or the absence of menstruation at puberty. In the context of CAIS, this is due to the absence of a uterus and other female reproductive structures that aid in menstruation such as ovaries (NHS, 2021) (Ovidiu et al., 2022).

After the diagnosis of primary amenorrhea, if CAIS is suspected, then a medical professional may look for common CAIS traits. At puberty, adolescent girls with CAIS often have little to no pubic or axillary hair, but generally have normal breast development. However, this is thought to be the result of lack of androgen action rather than the result of increased levels of estrogen, since their levels of estrogen are like that of typical males. Additionally, girls with CAIS tend to be taller than average XX females, but shorter than average XY males. Since during fetal development AMH caused the regression of the Mullerian ducts, girls with CAIS do not have a cervix or uterus, resulting in a short and blind-ended vagina. Due to a lack of testicular development, women with CAIS are infertile (NHS, 2021) (Ovidiu et al., 2022).

To confirm a diagnosis of CAIS then a karyotype assessment is recommended to see if the child has XY or XX sex chromosomes. Imaging investigations can also be conducted to see whether the child has internal genitalia such as a uterus, fallopian tubes, and ovaries. In the case of CAIS, internal reproductive structures will be absent, except for testes, meaning that they are infertile. Additionally, hormone levels such as luteinizing hormone (LH), follicle stimulating hormone (FSH), sexual hormone binding globulin (SHBG), and testosterone can be examined. In CAIS, LH concentrations are marginally higher than in normal XY males. FSH, SHBG, and estrogen concentrations are often at normal levels for XY men. Lastly, testosterone is often at a normal value as seen in typical XY males, despite the AR being unable to detect it.

Partial androgen insensitivity syndrome (PAIS) is the result of androgen receptors that have an incomplete or partial insensitivity to androgens. This can result in PAIS infants having partially virialized or ambiguous external genitalia at birth, depending on the AR degree of insensitivity. Consequently, PAIS is generally identified at birth since ambiguous or atypical external genitalia complicates sex assignment. Currently, it is thought that since infants with PAIS have partial virilization of the external genitalia, then their brain is also partially virialized. However, sex assignment is generally based on the extent of virilization. For example, if an infant with PAIS has mild virilization they may be assigned male whereas an infant may be assigned female if their genitals are closer to being ambiguous. Individuals with PAIS are often raised as boys, however, 25% of individuals with PAIS who are raised as boys have a self-initiated gender change later in life while 15% of individuals who are raised as girls have rate of self-initiated gender change (Sandberg and Gardner, 2022).

The process of confirming a PAIS diagnosis is like that of CAIS. In terms of hormone concentration, newborns with PAIS often have high levels of LH, testosterone, and estrogen. Infants with PAIS who are assigned male at birth may have hypospadias, where the urethral opening is located on the underside of the penis. This can be surgically corrected, however individuals who are assigned female at birth will not require this surgery. At puberty, adolescents with PAIS often have sparse pubic and axillary hair and may experience some breast development. Men with PAIS typically have fertility issues due to a severe lack of sperm production and require assisted contraception treatments, however, there have been cases where spontaneous fertility has occurred without the assistance of fertility treatments (Sultan et al., 2002) (NHS, 2021) (Ovidiu et al., 2022) (Lucas-Herald et al., 2016).

Mild androgen insensitivity syndrome is marked by a minor degree of AR insensitivity. Infants with MAIS are not normally diagnosed at birth as they almost always have a male phenotype, meaning their external genitalia is fully or mostly virialized. As a result, they are often assigned male at birth in addition to maintaining a male gender identity later in life. While individuals with MAIS do not have under-virialized genitalia, they may have under-virialized secondary sex characteristics. During puberty, adolescent boys with MAIS may have reduced pubic hair and axillary hair, impaired spermatogenesis, and gynecomastia (increased breast tissue). The diagnosis of MAIS is generally made when men with the syndrome seek medical advice for infertility. The diagnostic options can be similar to the other forms of AIS, however hormone testing and genetic assessment to examine possible AR mutations is likely to take precedent over other diagnostic methods. An additional indicator of MAIS is Kennedy's disease, which affects motor neurons (NIH, 2022) (Ovidiu et al., 2022) (Rapheal et al., 2022).

### **Treatment**

The main treatment options for CAIS include gonadectomy, hormone replacement therapy, and vaginal dilation. Women with CAIS have a prostate but are virtually at no risk of developing prostate cancer due to lack of prostate development, however they are

at risk for gonadal cancer (Ovidiu et al., 2022). After the diagnosis of CAIS the option of a gonadectomy may be presented at an early age to mitigate the risk of malignancy. However, gonadectomy in children with CAIS is controversial, as the risk of developing a germ cell tumor before the age of 30 can be as low as 0.02%. Only after the age of 30 does the risk increase to around 22%. Since the risk of cancer is low, some feel that gonadectomy should be postponed until after puberty or when the individual can decide for themselves if they want their testes removed (Tyutyusheva et al., 2021) (Batista et al., 2018). If a gonadectomy occurs before puberty, then estrogen replacement therapy will be needed to start puberty. However, if the testes are maintained then this is not necessary and typical female secondary characteristics will occur, such as breast development (Gottlieb and Trifiro, 2017). Genitoplasty is not needed as women with CAIS have typical female external genitalia, however vaginal dilation is an option for patients who want to be sexually active (Batista et al., 2018). Due to the effects that androgens have on bone development, women with CAIS may be at risk for weakened bone density, which increases the risk of fractures. Despite this, women with CAIS do not seem to have higher than average rates of osteoporosis, when compared to XX females. Overall, women with CAIS are expected to have a normal life span (Khatun and Rahman, 2015) (Berglund et al., 2017).

In children with PAIS who are raised as boys, it is recommended to surgically move the undescended testes to the scrotum as soon as possible to prevent the risk of hernias. Individuals with PAIS produce testosterone, however, to promote virilization testosterone and DHT are often prescribed. If a gonadectomy has occurred, then hormone replacement therapy with testosterone will be needed to start puberty (Batista et al., 2018). Additionally, boys with PAIS may have their urethral meatus (urethral opening) located at the underside of their penis, which can be surgically moved to the glans. In children with PAIS who are raised as girls, genitoplasty is recommended as the external genitalia is partially virialized or under-feminized. Similar to women with CAIS, vaginal dilation is an option for women with PAIS who are interested in being sexually active. Additionally, hormone replacement therapy using estrogen is needed to start puberty in the case of gonadectomy. As adults, women with PAIS may elect to reduce the size of their clitoris. Since their clitoris was partially virialized, it may be larger than in typical women and may have increased sensitivity, which can cause sex to be uncomfortable (NHS, 2021) (Ovidiu et al., 2022).

Men with MAIS who have impaired spermatogenesis can achieve fertility through hormone replacement therapy using high doses of androgens. During puberty, it is common for adolescents with MAIS to develop gynecomastia (increases breast tissue in men). Depending on the severity, surgery is often recommended to eliminate excess breast tissue (Batista et al., 2018). As the result of AR mutation, it is common for individuals with MAIS to have Kennedy's disease, a recessive X-linked disease, characterized by: spinal muscular atrophy, dysphagia, speaking difficulties, gynecomastia, and infertility (Ovidiu et al., 2022). The treatment for Kennedy's disease is limited to symptom management and physical therapy to improve muscle weakness may help (Greenland and Zajac, 2004)



(NIH, 2022). Regardless of the possible comorbidity of MAIS and Kennedy's disease, men with MAIS are expected to have a normal life expectancy (Rafael et al., 2022).

### Psychosocial Outcomes

Stigma is a significant issue in the context of DSDs, AIS included. It is not uncommon for parents of a child with AIS to have little to no knowledge about AIS or DSD in general, prior to their child's diagnosis. However, even after diagnosis, many families report that medical communication regarding their child's condition was lacking due to an abundance of medical terminology and/or little disclosure about the condition itself. Since DSDs often contradict cultural norms/understanding of biological sex, this can be distressing to parents who often feel in the dark about what AIS entails as well as fear of stigma and withdrawal of support systems. In an effort to avoid the child experiencing psychological distress or anticipated social stigma, parents may choose to keep their child's condition a secret from close family members, including siblings of the child, and the child themselves. However, this can unintentionally have the opposite effect, conveying the message that their condition is unnatural and something to be ashamed of (Sandberg and Gardner, 2022) (Garrett and Kirkman, 2009).

To mitigate anticipated stigma, parents may elect to have their child undergo early genital surgery, also referred to as genital normalization surgery, which is a cosmetic surgery intended to lessen the chance of psychological distress for the individual with AIS. While early genital surgery may appear to be straightforward, it is a complex and controversial topic. The most disputed genital normalization surgery is urogenital surgery, due to reports of individuals who have experienced significant complications from the procedure. In the context of PAIS, where 25% of individuals who are assigned male at birth have a self-initiated gender change, it is argued that cosmetic genital surgeries with permanent effects, such as urogenital surgery, should be deferred until the individual's gender is more certain. For these reasons, many activist groups suggest that this surgery should be delayed until the individual is old enough to give informed consent before choosing to get the surgery or not. Despite the severity of complications when this procedure is not successful, most individuals who have had urogenital surgery at a young age are satisfied with the outcomes and do not agree that it should be deferred later in life (Sandberg and Gardner, 2022) (Jorge et al., 2021).

In the case of women with AIS, while genital normalization surgery is not always recommended, the alternatives are not always favorable. Vaginal dilators are meant to be a safer, patient controlled, and less painful alternative to vaginoplasty. Some women with AIS report that they were not prepared for the pain or discomfort that the vaginal dilators caused. Additionally, some report that the reason behind the treatment was not always explained by their healthcare team (Elschlager and Appelbaum 2016) (Sandberg and Gardner, 2022). Anderson and colleagues found that lack of adherence to treatment was not uncommon among their participants with AIS, possibly due to lack of medical communication as well as doctors not taking the psychological impact of the treatments into account. Infact none of their participants who were prescribed vaginal dilators as

teenagers were able to use them properly. Additionally, some reported that they had a low adherence to HRT as the reasoning behind the treatment was not thoroughly explained and participants reported just wanting to feel normal (Alderson et al., 2004).

Women with CAIS have increased risk of psychiatric morbidity (Enberg et al., 2017), however this does not always seem to be associated with their infertility. In 2016 Fliegner et al. found that individuals with CAIS on average had a low wish for children and the thought of having biological children rarely crossed their mind. This result was contrasted with infertile women who had a different DSD. Adoption is currently the only way women with CAIS can become mothers, however with future medical advancements it may be possible to collect the gametes of women with CAIS, making parenthood possible, further adding to the controversy surrounding gonadectomy in individuals with CAIS. Psychological distress is more commonly found in people with PAIS, where around 25% of individuals experience significant dissatisfaction with their assigned sex or experience. This is contrasted in women with CAIS who often experience doubts regarding their femininity after diagnosis, but still consistently identify with their assigned gender (Pritsini et al., 2017).

## DISCUSSION

People with AIS are expected to have normal lifespans. However, women with CAIS are at risk of germ cell tumors and weakened bone density, while men with MAIS frequently have Kennedy's disease. The diagnostic process of AIS can include investigating family history, and genetic and hormone testing. Sex assignment is straight forward in individuals with CAIS and MAIS with their respective female and male phenotype, however this is not the case with individuals with PAIS where higher rates of self-initiated gender change occur later in life.

Treatment options for AIS can include hormone replacement therapy using either estrogen or androgens depending on the specific AIS category, as well as cosmetic and non-cosmetic surgeries to restore function to the external genitalia or to normalize the appearance. Gender normalization surgeries are a disputed topic. This is due to the ethical concerns regarding a largely permanent cosmetic surgery that carries risk of chronic pain or discomfort as well as issues regarding lack of informed consent, notably regarding DSDs with higher rates of self-initiated gender change. Additionally, treatment options such as HRT can have low rates of adherence when there is a lack of transparency as to what the treatment's purpose is and if it is wanted by the patient in the first place.

People with AIS are at risk of psychological morbidity or distress due to stigma, shame, as well as lack of doctor-patient communication within the healthcare industry. Lack of communication and transparency between healthcare teams, patients, and families of patients with AIS may be a contributing factor to the stigma and psychological distress regarding this DSD. There is a need for more research regarding mental health outcomes in individuals with AIS as the sample sizes are often small due to the rarity of the condition as well as a lack of studies in general.

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