

Syndromes of Abnormal Sex Differentiation

A guide for patients and their families



The Johns Hopkins Children's Center

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I. Introduction

Sexual differentiation is a complex process which results in a newborn baby who is either male or female. If errors in development occur, sexual development is abnormal and the sex organs of the baby are malformed. In such cases, individuals may develop both male and female characteristics. This is referred to as intersexuality.

Children born with deviations from normal development of the sex organs can be expected to grow up successfully and to lead enriched lives. However, their problems must be considered carefully. In cases of abnormal sex differentiation, efforts should be made to determine the reason for the abnormality as treatment may vary according to the cause of the disorder. There may also be a need for specific surgical repair and/or hormonal therapy. Finally, it is extremely important for parents and patients to have a good understanding of both the condition of sex differentiation that affects them, as well as possible ways for dealing with the condition. With this approach, patients will be better able to lead a fulfilled life, and to look forward to an education, career, marriage, and parenthood.

This booklet has been prepared to help parents and patients better understand intersexuality and the unique challenges that accompany syndromes of abnormal sex differentiation. We believe that informed individuals are better prepared to face these challenges and are more likely to meet successfully the demands of childhood, adolescence, and adulthood.

First, normal sex differentiation will be described. The understanding of this pattern of development will help patients and their families to understand the problems of ambiguous sex differentiation, which are subsequently outlined. Finally, a glossary of terms and a list of helpful support groups are provided.

II. Normal Sex Differentiation

Human sexual differentiation is a complicated process. In a simple manner, one can describe four major steps which constitute normal sexual differentiation. These four steps are:

1. Fertilization and determination of genetic sex
2. Formation of organs common to both sexes
3. Gonadal differentiation
4. Differentiation of the internal ducts and external genitalia

Step 1: Fertilization and Determination of Genetic Sex

The first step of sex differentiation takes place at fertilization. An egg from the mother, which contains 23 chromosomes (including an X chromosome), is combined with a sperm from the father, which also contains 23 chromosomes (including either an X or Y chromosome). Therefore, the fertilized egg has either a 46,XX (genetic female) or 46,XY (genetic male) karyotype.

Step 1 in sex differentiation:
Determination of genetic sex
Egg (23,X) + Sperm (23,X) = 46,XX genetic girl
OR
Egg (23,X) + Sperm (23, Y) = 46, XY genetic boy

Step 2: Formation of Organs Common to Both Sexes

The fertilized egg multiplies to form a large number of cells, all of which are similar to each other. However, at specific times during the growth of an embryo, the cells differentiate to form the various organs of the body. Included in this development is the differentiation of the sex organs. At that stage, both 46,XX and 46,XY fetuses have similar sex organs, specifically:

- a. the gonadal ridges
- b. the internal ducts
- c. the external genitalia

a. The gonadal ridges can be easily recognized by 4-5 weeks of gestation. At that time, they already include the undifferentiated germ cells which will later develop into either eggs or sperm. The formation of gonadal ridges similar in both sexes is a prerequisite step to the development of differentiated gonads. This organization of cells into a ridge requires the effects of several genes, such as SF-1, DAX-1, SOX-9, etc. If any one of these genes is non-functional, then there is no formation of a gonadal ridge and therefore no formation of either testes or ovaries.

b. By 6-7 weeks of fetal life, fetuses of both sexes have two sets of internal ducts, the Mullerian (female) ducts and the Wolffian (male) ducts.

c. The external genitalia at 6-7 weeks gestation appear female and include a genital tubercle, the genital folds, urethral folds and a urogenital opening. (see Figure 2)

Step 3: Gonadal Differentiation

The important event in gonadal differentiation is the commitment of the gonadal ridge to become either an ovary or a testis.

a. In males, the gonadal ridge develops into testes as a result of a product from a gene located on the Y chromosome. This product has been termed the "testis determining factor" or "sex determining region of the Y chromosome" (SRY).

b. In females, the absence of SRY, due to the absence of a Y chromosome, permits the expression of other genes which will trigger the gonadal ridge to develop into ovaries.

Step 3 in Sex Differentiation:
Determination of Gonadal Sex
XX fetus = ovary
(with no SRY)
OR
XY fetus = testes
(with SRY located on the Y chromosome)

Step 4: Differentiation of the Internal Ducts and External Genitalia

The next step in sex differentiation depends upon the formation of two important hormones: the secretion of Mullerian (female) Inhibiting Substance (MIS) and the secretion of androgens.

If testes are developing normally, then Sertoli cells of the developing testes produce MIS which inhibits the growth of the female Mullerian ducts (the uterus and fallopian tubes) which are present in all fetuses early in development. Additionally, the Leydig cells of the testes start secreting androgens. Androgens are hormones that produce growth effects on the male Wolffian ducts (the epididymis, vas deferens, seminal vesicles) which are also present in all fetuses early in development.

Unlike the testes, the ovaries do not produce androgens. As a result, the Wolffian ducts fail to grow and consequently disappear in fetuses with ovarian development. In addition, the ovaries do not produce MIS at the appropriate time, and as a consequence, the Mullerian (female) ducts can develop.

In other words, two products of the developing testes are needed for normal male development. First, MIS must be secreted to inhibit female duct growth and androgens must be secreted to enhance male duct growth. In contrast, a female fetus with no developing testes will produce neither MIS nor androgens, and hence female ducts will develop and male ducts will disappear.

Step 4 in Sex Differentiation: Determination of Internal Ducts
Males
Testes produce MIS = inhibit female development
Testes produce androgens = enhance male development
OR
Females
Ovaries do not produce MIS = enhance female development

Ovaries do not produce androgens = inhibit male development

External Genitalia

In the female, absence of androgens permits the external genitalia to remain feminine: the genital tubercle becomes the clitoris, the genital swellings become the labia majora and the genital folds become the labia minora.

In the male, fetal androgens from the testes masculinize the external genitalia. The genital tubercle grows to become the penis and the genital swellings fuse to form the scrotum.

- genetic sex is determined
- testes develop in XY fetus, ovaries develop in XX fetus
- XY fetus produces MIS and androgens and XX fetus does not
- XY fetus develops Wolffian ducts and XX fetus develops Mullerian ducts
- XY fetus masculinizes the female genitalia to make it male and the XX fetus retains female genitalia

Summary of Normal Sex Differentiation

- genetic sex is determined
- testes develop in XY fetus, ovaries develop in XX fetus
- XY fetus produces MIS and androgens and XX fetus does not
- XY fetus develops Wolffian ducts and XX fetus develops Mullerian ducts
- XY fetus masculinizes the female genitalia to make it male and the XX fetus retains female genitalia

III. Disorders of Sex Differentiation - A General Outline

Sex differentiation is a complex physiological process comprised of many steps. Problems associated with sex differentiation, or syndromes of intersexuality, occur when errors in development take place at any of these steps.

Genetic Sex

Problems can arise at fertilization when chromosomal sex is established. For example, girls with Turner Syndrome have a 45,XO karyotype and boys with Klinefelter Syndrome have a 47,XXY karyotype. It is also known that some women have a 46,XY or 47,XXX karyotype and some men a 46,XX or 47,XYY karyotype. Clearly then, when it is stated that 46,XY refers to male sex and 46,XX refers to female sex, this is a generalization which applies to most, but not all, individuals.

Gonadal Sex

Disorders of sex differentiation can occur when a bipotential gonad is incapable of developing into a testis or an ovary. The inability to develop testes may occur if a gene such as SRY is absent or deficient. When this is the case, a 46,XY fetus will not receive the SRY signal to develop testes despite the presence of a Y chromosome. Additionally, 46,XY fetuses may begin to develop testes, but this development can be thwarted, and subsequently MIS and androgen production may be absent or diminished.

Finally, the normal disappearance of germ cells associated with ovarian development in fetuses is so accelerated in Turner Syndrome that by birth these babies possess gonadal streaks as opposed to normal ovaries.

Mullerian and Wolffian Duct Development

Intersexuality can also result as a consequence of problems related to Mullerian or Wolffian duct development. For example, MIS secretion accompanied by the absence of androgens or the inability to respond to androgens can result in a fetus lacking both male and female internal duct structures. In contrast, the absence of MIS accompanied by androgen secretion can result in a fetus possessing both male and female internal duct structures to varying degrees.

External Genitalia

Babies born with sex differentiation syndromes possess external genitalia that can usually be classified as either:

1. normal female
2. ambiguous

3. normal male but with a very small penis (micropenis)

Normal female external genitalia develop among 46,XY intersex patients when the genital tubercle, genital swellings, and genital folds either completely lack exposure to, or are totally incapable of responding to, male hormones. As a result, masculinization of the external genital structures is not possible. In such cases, the genital tubercle develops into a clitoris, the genital swellings develop into the labia majora and the genital folds develop into the labia minora.

Ambiguous external genitalia develop in female patients when the external genital structures are exposed to greater-than-normal amounts of male hormones (masculinized females) or in male patients when less-than-normal amounts of male hormones (under-masculinized males) occurs. Thus, in these patients, external genitalia develop in a manner that is neither female nor male, but rather is somewhere in between the two.

For instance, patients with ambiguous external genitalia may possess a phallus which ranges in size from resembling a large clitoris to a small penis. Additionally, these patients may possess a structure that resembles partially fused labia or a split scrotum. Finally, patients with ambiguous external genitalia often possess a urethral (urinary) opening that is not at the tip of the phallus (normal male position), but is instead located elsewhere on the phallus or perineum. The atypical positioning of the urethra in such instances is referred to as hypospadias.

Babies born with a penis that is much smaller than normal (micropenis) have a completely normal appearing external genitalia (i.e.), the urethra is properly located at the tip of the phallus and the scrotum is completely fused). However, the size of the phallus is closer to that of a normal clitoris than a normal penis.

IV. Specific Syndromes of Sex Differentiation

1. Androgen Insensitivity Syndrome (AIS)

Androgen Insensitivity Syndrome occurs when an individual, due to a mutation of the androgen receptor gene, is incapable of responding to androgens. Two forms of AIS exist, Complete AIS (CAIS) and Partial AIS (PAIS).

CAIS

CAIS affects 46,XY individuals. CAIS patients have normal appearing female external genitalia due to their complete inability to respond to androgens. This is because the genital tubercle, genital swellings, and genital folds can not masculinize in these patients despite the presence of functional testes located in the abdomen. Similarly, Wolffian duct development does not occur because the Wolffian duct structures can not respond to androgens produced by CAIS patients. Mullerian duct development is inhibited in CAIS individuals because MIS is secreted by the testes.

In addition to possessing normal female external genitalia, CAIS individuals also experience normal female breast development along with sparse pubic and axillary hair growth at puberty. The following chart illustrates the steps of sex differentiation associated with CAIS compared to those of unaffected males and females.

Normal Female Development	CAIS Development	Normal Male Development
XX	XY	XY
ovaries develop	testes develop	testes develop
no androgen produced	androgen produced, but body can not respond	androgen produced
Wolffian Ducts regress	Wolffian Ducts regress	Wolffian Ducts develop
no MIS produced	MIS produced	MIS produced
Mullerian Ducts develop	Mullerian Ducts do not develop	Mullerian Ducts do not develop
external genitalia are female	external genitalia are female	external genitalia are male
feminizing puberty	feminizing puberty without menses	masculinizing puberty

PAIS

PAIS also affects 46,XY individuals. PAIS patients are born with ambiguous external genitalia due to their partial inability to respond to androgens. The genital tubercle is larger than a clitoris but smaller than a penis, a partially fused labia/scrotum may be present, the testes may be undescended, and perineal hypospadias is often present. Wolffian duct development is minimal or nonexistent and the Mullerian duct system does not develop properly.

PAIS patients will experience normal female breast development at puberty, along with a small amount of pubic and axillary hair. The chart on the following page illustrates the steps of sex differentiation associated with PAIS compared to those of unaffected males and females.

Normal Female Development	PAIS Development	Normal Male Development
XX	XY	XY
ovaries develop	testes develop	testes develop
no androgen produced	androgen produced, but body partially unresponsive	androgen produced
Wolffian Ducts regress	Wolffian Ducts develop minimally	Wolffian Ducts develop
no MIS produced	MIS produced	MIS produced
Mullerian Ducts develop	Mullerian Ducts do not develop	Mullerian Ducts do not develop
external genitals are female	external genitalia are ambiguous	external genitalia are male
feminizing puberty	partial masculinizing puberty with testosterone therapy OR feminizing puberty with estrogen therapy	masculinizing puberty

2. Gonadal Dysgenesis

Unlike AIS in which affected individuals possess functioning testes but can not respond to the androgens their testes produce, patients with Gonadal Dysgenesis can respond to androgens but develop abnormal testes which are incapable of producing androgens. Like AIS, two forms of Gonadal Dysgenesis exist (Complete and Partial).

Complete Gonadal Dysgenesis

Complete Gonadal Dysgenesis affects 46,XY individuals and is characterized by abnormally formed gonads which were originally on the path to testis differentiation (these abnormally formed gonads are referred to as gonadal streaks), female external genitalia, Mullerian duct development, and Wolffian duct regression. Female external genitalia develop due to the failure of the gonadal streaks to produce androgens necessary to masculinize the genital tubercle, genital swellings, and genital folds. Additionally, because the gonadal streaks are incapable of producing either androgens or MIS, the Wolffian duct system regresses while the Mullerian duct system develops. The following chart illustrates the steps of sex differentiation associated with Complete Gonadal Dysgenesis compared to those of unaffected males and females.

Normal Female Development	Complete Gonadal Dysgenesis	Normal Male Development
XX	XY	XY
ovaries develop	streak gonads	testes develop
no androgen produced	no androgen produced	androgen produced
Wolffian Ducts regress	Wolffian Ducts regress	Wolffian Ducts develop
no MIS produced	no MIS produced	MIS produced
Mullerian Ducts develop	Mullerian Ducts develop	Mullerian Ducts regress
external genitalia are female	external genitalia are female	external genitalia are male
feminizing puberty	feminizing puberty with estrogen therapy	masculinizing puberty

Partial Gonadal Dysgenesis

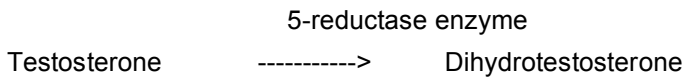
Partial Gonadal Dysgenesis also affects 46,XY individuals, and this condition is characterized by partial testes determination usually accompanied by ambiguous external genitalia at birth. Affected patients may have a combination of Wolffian and Mullerian duct development. The combination of both Wolffian and Mullerian duct development, along with ambiguity of the external structures, indicates that the testes produced more androgens and MIS than those of Complete Gonadal Dysgenesis patients, but not as much as would be seen in normal male development. The chart on the following page illustrates the steps of sex differentiation associated with Partial Gonadal Dysgenesis compared to those of unaffected males and females.

Normal Female Development	Partial Gonadal Dysgenesis	Normal Male Development
XX	XY	XY
ovaries develop	partial testes determination	testes develop
no androgen produced	variable amount of androgen produced	androgen produced
Wolffian Ducts regress	some Wolffian Duct development	Wolffian Ducts develop
no MIS production	variable amount of MIS production	MIS production
Mullerian Ducts develop	some Mullerian Duct development	Mullerian Ducts do not develop
external genitalia are female	ambiguous external genitalia	external genitalia are male
feminizing puberty	feminizing puberty with estrogen therapy OR masculinizing puberty with testosterone therapy	masculinizing puberty

3. 5-Reductase Deficiency

During fetal development, the genital tubercle, genital swellings, and genital folds masculinize when exposed to androgens. Androgens, or male hormones, are a general term for two specific hormones Ñ testosterone and dihydrotestosterone (DHT). DHT is a stronger androgen than

testosterone, and DHT is formed when the enzyme 5 α -Reductase converts testosterone to DHT.



5-Reductase deficiency affects 46,XY individuals. During fetal development, the gonads differentiate into normal testes, secrete appropriate amounts of testosterone, and patients are able to respond to this testosterone. However, affected individuals are unable to convert testosterone to DHT, and DHT is necessary for the external genitalia to masculinize normally. The result is a newborn baby with functioning testes, normally developed Wolffian ducts, no Mullerian ducts, a penis resembling a clitoris, and a scrotum resembling labia majora.

At puberty, testosterone (not DHT), is the essential androgen for masculinization of the external genitalia. Therefore, stereotypical signs of masculine pubertal development will be observed in patients. These signs include an increase in muscle mass, lowering of the voice, growth of the penis (although it is unlikely that it will reach a normal male length), and sperm production if the testes remain intact. These patients have a fair amount of pubic or axillary hair growth, but they have little or no facial hair. They do not experience female breast development. The following

chart illustrates the steps of sex differentiation associated with 5 α -Reductase Deficiency compared to those of unaffected males and females.

Normal Female Development	5-Reductase Deficiency	Normal Male Development
XX	XY	XY
ovaries develop	testes develop	testes develop
no androgen produced	testosterone but no DHT produced	androgen produced
Wolffian Ducts regress	Wolffian Ducts develop	Wolffian Ducts develop
no MIS produced	MIS produced	MIS produced
Mullerian Ducts develop	Mullerian Ducts regress	Mullerian Ducts regress
external genitalia are female	ambiguous external genitalia	external genitalia are male
feminizing puberty	testes left intact, partial masculinizing puberty OR feminizing puberty with removal of testes and estrogen therapy	masculinizing puberty

4. Testosterone Biosynthetic Defects

Testosterone is produced from cholesterol through a number of biochemical conversions. In some individuals, one of the enzymes needed for these conversions is deficient. In such cases, patients are unable to make normal amounts of testosterone despite the presence of testes. Testosterone Biosynthetic Defects affect 46,XY individuals and can be complete or partial, which

leads to newborns who appear either completely female or ambiguous, respectively. Four Testosterone Biosynthetic Defects are listed below:

- a. Cytochrome P450,CYP11A Deficiency
- b. 3 β -Hydroxysteroid Dehydrogenase Deficiency
- c. Cytochrome P450,CYP17 Deficiency
- d. 17-Ketosteroid Reductase Deficiency

The first three enzyme deficiencies listed above result in Congenital Adrenal Hyperplasia (CAH) (described later) as well as decreased testosterone production by the testes. The fourth enzyme, 17-Ketosteroid Reductase Deficiency, is not associated with CAH. The following chart illustrates the steps of sex differentiation associated with Testosterone Biosynthetic Defects compared to those of unaffected males and females.

Complete Biosynthetic Defect

Normal Female Development	Complete Testosterone Biosynthetic Defect	Normal Male Development
XX	XY	XY
ovaries develop	testes develop	testes develop
no androgen produced	no androgens due to enzyme deficiency	androgen produced
Wolffian Ducts regress	Wolffian Ducts regress	Wolffian Ducts develop
no MIS is produced	MIS is produced	MIS is produced
Mullerian Ducts develop	Mullerian Ducts regress	Mullerian Ducts regress
external genitalia are female	external genitalia are female	external genitalia are male
feminizing puberty	feminizing puberty if given estrogen therapy	masculinizing puberty

Partial Biosynthetic Defect

Normal Female Development	Partial Testosterone Biosynthetic Defect	Normal Male Development
XX	XY	XY
ovaries develop	testes develop	testes develop
no androgen produced	partial production of androgens	androgen produced
Wolffian Ducts regress	some Wolffian Duct development	Wolffian Ducts develop
no MIS produced	MIS produced	MIS produced
Mullerian Ducts develop	Mullerian Ducts regress	Mullerian Ducts regress
external genitalia are female	ambiguous external genitalia	external genitalia are male
feminizing puberty	partial masculinizing puberty with testosterone therapy OR feminizing puberty with estrogen therapy	masculinizing puberty

5. Micropenis

Androgens are necessary at two different points in fetal development for a normal penis to form: (1) early in fetal life to masculinize the genital tubercle, genital swellings, and genital folds into a penis and scrotum, and (2) later in fetal life to enlarge the penis. Individuals with a micropenis possess a normally developed penis, except that the penis is extremely small. The condition of micropenis is thought to occur in 46,XY individuals if androgen production is insufficient for penile growth after the first part of masculinization of the external genitalia has already occurred. The chart on the following page illustrates the steps of sex differentiation associated with micropenis compared to those of unaffected males and females.

Normal Female Development	Micropenis	Normal Male Development
XX	XY	
ovaries develop	testes develop	testes develop
no androgen produced	androgens early in fetal life, deficient later in fetal life	androgen produced
Wolffian Ducts regress	Wolffian Ducts develop	Wolffian Ducts develop
no MIS produced	MIS produced	MIS produced
Mullerian Ducts develop	Mullerian Ducts regress	Mullerian Ducts regress
external genitalia are female	micropenis	external genitalia are male
feminizing puberty	partially masculinizing puberty if exposed to testosterone OR feminizing puberty if given estrogen therapy	masculinizing puberty

6. Timing Defect

The many steps of sex differentiation are further complicated by the fact that proper timing of these steps is necessary for normal development. If all of the steps required for male sex differentiation are working, yet these steps are delayed by even a few weeks, the result can be ambiguous differentiation of the external genitalia in a 46,XY individual. The following chart illustrates the steps of sex differentiation associated with a Timing Defect compared to those of normal males

Normal Female Development	Timing Defect	Normal Male Development
XX	XY	XY
ovaries develop	testes develop	testes develop
no androgen produced	androgen produced at incorrect time	androgen produced

Wolffian Ducts regress	Wolffian Ducts develop	Wolffian Ducts develop
no MIS produced	MIS produced	MIS produced
Mullerian Ducts develop	Mullerian Ducts regress	Mullerian Ducts regress
external genitalia are female	external genitalia range from female to ambiguous	external genitalia are male
feminizing puberty	partially masculinizing puberty with testosterone therapy OR feminizing puberty with estrogen therapy	masculinizing puberty

7. Congenital Adrenal Hyperplasia (CAH) in 46,XX Individuals

In CAH excess adrenal androgens are produced as an indirect result of a cortisol biosynthetic defect (by far the most frequent defect is a cytochrome P450, CYP21 deficiency). In 46,XX individuals, excess adrenal androgens can lead to ambiguous development of the external genitalia, so that these babies have an enlarged clitoris and a fused labia which resembles a scrotum. The chart on the following page illustrates the steps of sexual differentiation associated with 46,XX CAH (21-hydroxylase deficiency) individuals compared to those of unaffected males and females.

Normal Female Development	46,XX CAH	Normal Male Development
XX	XX	XY
ovaries develop	ovaries develop	testes develop
no androgen produced	no testicular androgens but excessive adrenal androgens produced	androgen produced
Wolffian Ducts regress	Wolffian Ducts regress	Wolffian Ducts develop
no MIS produced	no MIS produced	MIS produced
Mullerian Ducts develop	Mullerian Ducts develop	Mullerian Ducts regress
external genitalia are female	ambiguous external genitalia	external genitalia are male
feminizing puberty	feminizing puberty if treated with cortisol	masculinizing puberty

8. Klinefelter Syndrome

Klinefelter Syndrome is the term given to individuals with a 47,XXY karyotype. At puberty Klinefelter men can experience female breast growth, low androgen production, small testes, and decreased sperm production. Additionally, although Klinefelter men undergo normal male differentiation of the external genitalia, they often possess a penis that is smaller than that of normal men. The following chart illustrates the steps of sexual differentiation associated with individuals who have Klinefelter Syndrome, compared to those of unaffected males and females.

Normal Female Development	Klinefelter Syndrome	Normal Male Development
XX	XXY	XY
ovaries develop	small testes at puberty	testes develop
no androgen produced	often decreased androgen production	androgen produced
Wolffian Ducts regress	Wolffian Ducts develop	Wolffian Ducts develop
no MIS produced	MIS produced	MIS produced
Mullerian Ducts develop	Mullerian Ducts regress	Mullerian Ducts regress
external genitalia are female	male external genitalia with small penis	external genitalia are male
feminizing puberty	masculinizing puberty with possible decreased androgen production	masculinizing puberty

9. Turner Syndrome

Turner Syndrome is the term given to individuals with a 45,XO karyotype. Turner patients can exhibit webbing of the neck, a broad chest, horseshoe kidneys, cardiovascular abnormalities, and short stature. Turner patients do not possess ovaries, but instead possess gonadal streaks. Turner patients have normal female external genitalia, but because they lack functioning ovaries (and thus the estrogens produced by ovaries) neither breast development, nor menstruation occurs spontaneously at puberty. The following chart illustrates the steps of sexual differentiation associated with Turner Syndrome compared to those of unaffected males and females.

Normal Female Development	Turner Syndrome	Normal Male Development
XX	XO	XY
ovaries develop	gonadal streaks develop	testes develop
no androgen produced	no androgen produced	androgen produced
Wolffian Ducts regress	Wolffian Ducts regress	Wolffian Ducts develop
no MIS produced	no MIS produced	MIS produced
Mullerian Ducts develop	Mullerian Ducts develop	Mullerian Ducts regress
external genitalia are female	external genitalia are female	external genitalia are male
feminizing puberty	feminizing puberty with estrogen therapy	masculinizing puberty

10. 45,XO/46,XY Mosaicism

Individuals born with 45,XO/46,XY Mosaicism can appear male, female, or ambiguous at birth. Males experience normal male sex differentiation and females are essentially identical to girls born with Turner Syndrome. For the purpose of this booklet, only patients with 45,XO/46,XY Mosaicism, who experience ambiguous sex differentiation, will be described on the following chart.

Mosaicism means that two or more sets of chromosomes influence the development of an individual. 45,XO/46,XY Mosaicism represents the most common mosaic condition involving the Y chromosome. Because the Y chromosome is affected, abnormal sex differentiation can result from this condition. The following chart illustrates the steps of sex differentiation associated with 45,XO/46,XY Mosaicism compared to those of unaffected males and females.

Normal Female Development	45,XO/46,XY Mosaicism	Normal Male Development
XX	XY	XY
ovaries develop	partial testes determination	testes develop
no androgen produced	variable amount of androgen produced	androgen produced
Wolffian Ducts regress	some Wolffian Duct development	Wolffian Ducts develop
no MIS production		MIS production
Mullerian Ducts develop	some Mullerian Duct development	Mullerian Ducts do not develop
external genitalia are female	ambiguous external genitalia	external genitalia are male
feminizing puberty	feminizing puberty with estrogen therapy OR masculinizing puberty with testosterone therapy	masculinizing puberty



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Syndromes of Abnormal Sex Differentiation

V. Summary

Sexual differentiation refers to the physiological development of a fetus along male or female lines. Disorders of sexual differentiation, or syndromes of intersexuality, result when errors occur at any of these steps. This booklet is organized to serve as a basic explanation of the process of normal sexual differentiation, and it is also meant to explain the deviations from normal development underlying several syndromes of sexual differentiation.