Puberty and Secondary Sexual Development

Osama Warda MD

Prof. of OBS/GYN

Mansoura university

The information included in this presentation are not the only source for this topic and you should explore other valuable references in order to satisfy the ILOs of this topic.

LEARNING OBJECTIVES

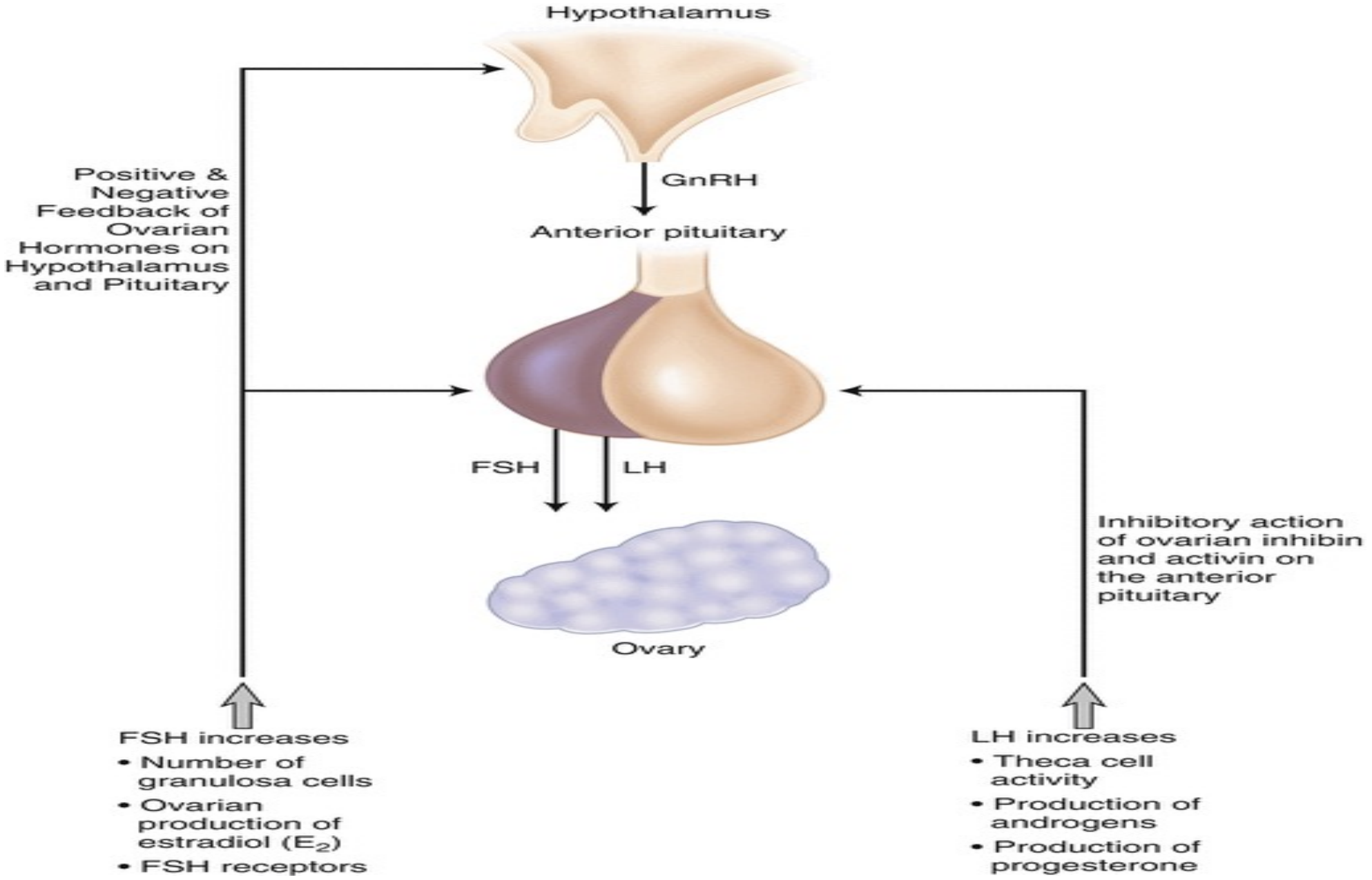
- Describe the normal changes of puberty and the secondary sexual differentiation that accompanies it.
- Understand the classification and causes of abnormal puberty and disorders of sexual development (DSD).

Normal puberty

- Puberty is the process of reproductive and sexual development and maturation that changes a child into an adult.
- During childhood, the HPO axis is suppressed and levels of GnRH, FSH and LH are very low.
- From the age of 8–9 years GnRH is secreted in pulsations of increasing amplitude and frequency. These are initially *sleep-related*, but as puberty progresses, these extend throughout the day.

Normal puberty

- This stimulates secretion of FSH and LH by the pituitary glands, which in turn triggers follicular growth and *steroidogenesis* in the ovary.
- The estrogen produced by the ovary then initiates the physical changes of puberty.
- The exact mechanism determining the onset of puberty is still unknown, but it is influenced by many factors including race, heredity, body weight and exercise.
- Leptin plays a permissive role in the onset of puberty.


Hypothalamus
GnRH
Anterior pituitary
Positive & Negative Feedback of Ovarian Hormones on Hypothalamus and Pituitary
FSH
LH
Ovary
Inhibitory action of ovarian inhibin and activin on the anterior pituitary
FSH increases
• Number of granulosa cells
• Ovarian production of estradiol (E_2)
• FSH receptors
LH increases
• Theca cell activity
• Production of androgens
• Production of progesterone

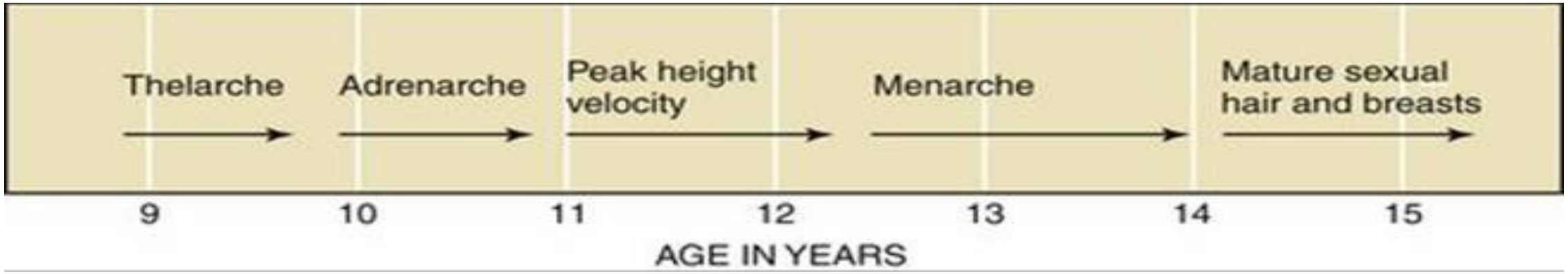
Pubertal events

1-Thelarche = Breast development

2-Adrenarche = pubic and axillary hair growth

3-Menarche = onset of menstruation

4-Growth spurt.



Pubertal events

- The first physical signs of puberty are breast budding and this occurs 2–3 years before menarche.
- The appearance of pubic hair is dependent on the secretion of adrenal androgens and is usually after thelarche.
- In addition to increasing levels of adrenal and gonadal hormones, growth hormone secretion also increases, leading to a pubertal growth spurt.

Pubertal events

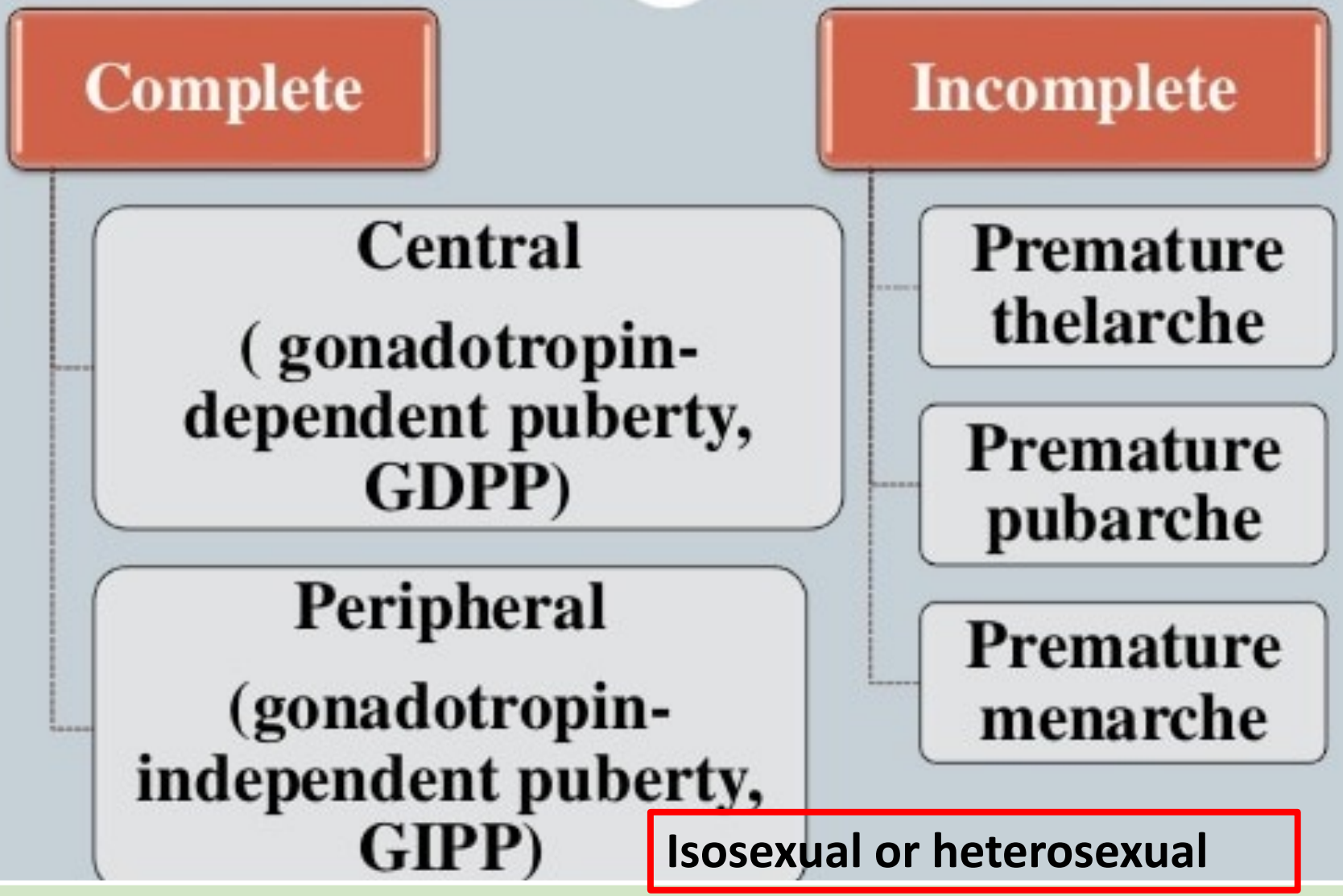
- The mean age of menarche is 12.8 years and it may take over 3 years before the menstrual cycle establishes a regular pattern.
- Initial cycles are usually anovulatory and can be unpredictable and irregular.
- The absence of menstruation is called amenorrhea and may be primary or secondary (refer to lecture of disorders of menstrual regularity). Pubertal development was described by Tanner ; breast & pubic hair stages 1-5, while axillary hair 1-3.

Tanner staging.

	1	2	3	4	5
Breast					
	Prepubertal	Breast and papilla are elevated as a small mound. Areolar diameter increases	Further enlargement of the breast bud with loss of the contour separation between breast and areola	Aerolar and papilla form a secondary mound	Mature areolar is part of the general breast contour
Pubic hair					
	Prepubertal	Sparse lightly pigmented chiefly along the medial border of the labia majora	Darker beginning to curl, increased amount spreading over the mons	Increased amount of course, curly but limited to the mons	Adult feminine triangle with spread to the medial surface of the thighs

Precocious puberty

- This is defined as *the onset of puberty before the age of 8 in a girl or 9 in a boy.*
- It is classified as either *central or peripheral*.
- Central precocious puberty is gonadotrophin dependent. The etiology is often unknown, although up to 25% are due to central nervous system (CNS) malformations or brain tumors.
- Peripheral precocious puberty, which is gonadotrophin independent, is always pathological and can be caused by estrogen secretion, such as exogenous ingestion or a hormone-producing tumor.


Complete
Incomplete
Central
(gonadotropin-dependent puberty, GDPP)
Peripheral
(gonadotropin-independent puberty, GIPP)
Premature thelarche
Premature pubarche
Premature menarche
Isosexual or heterosexual

Delayed puberty

- When there are no signs of secondary sexual characteristics by the age of 14 years this is termed delayed puberty.
- It is due to either a central defect (hypo-gonadotrophic hypogonadism) or a failure of gonadal function (hyper-gonadotrophic hypogonadism), which are described below.

Hypo- and hyper-gonadotrophic hypogonadism

Hypo-gonadotrophic hypogonadism

- This is central and may be constitutional, but other causes must be excluded: these include *anorexia nervosa*, *excessive exercise* and *chronic illness*, such as diabetes or renal failure. Rarer causes include a pituitary tumor and Kalman's syndrome.
- Associated with delayed puberty and primary amenorrhea (after 16ys).

Hypo- and hyper-gonadotrophic hypogonadism

Hyper-gonadotrophic hypogonadism

- This is caused by gonadal failure (The gonad does not function despite high gonadotrophins).
- Associated with *Turner syndrome and XX gonadal dysgenesis.*
- Premature ovarian failure can occur at any age, including prior to pubertal age, and may be idiopathic, but can also be part of an autoimmune or metabolic disorder or following chemo- or radiotherapy for childhood cancer.
- Associated with delayed puberty and primary amenorrhea.
- Hyper-gonadotrophic hypogonadism can also occur later in life and will cause secondary amenorrhea after normal sexual development.

Disorders of sexual development (DSD)

- DSD are conditions where the sequence of events described above does not happen.
- The clinical consequences of this depend upon where within the sequence the variation occurs.
- DSD may be diagnosed at birth with *ambiguous or abnormal genitalia*, but may also be seen at puberty in girls who present with *primary amenorrhea or increasing virilization*.

Summary of terminology for (DSD)

Previous intersex	Accepted DSD
Male pseudohermaphrodite	46, XY DSD
Undervirilization of XY male	
Undermasculinization of XY male	
Female pseudohermaphrodite	46 XX DSD
Overvirilization of an XX female	
Masculinization of an XX female	
True hermaphrodite	Ovotesticular DSD

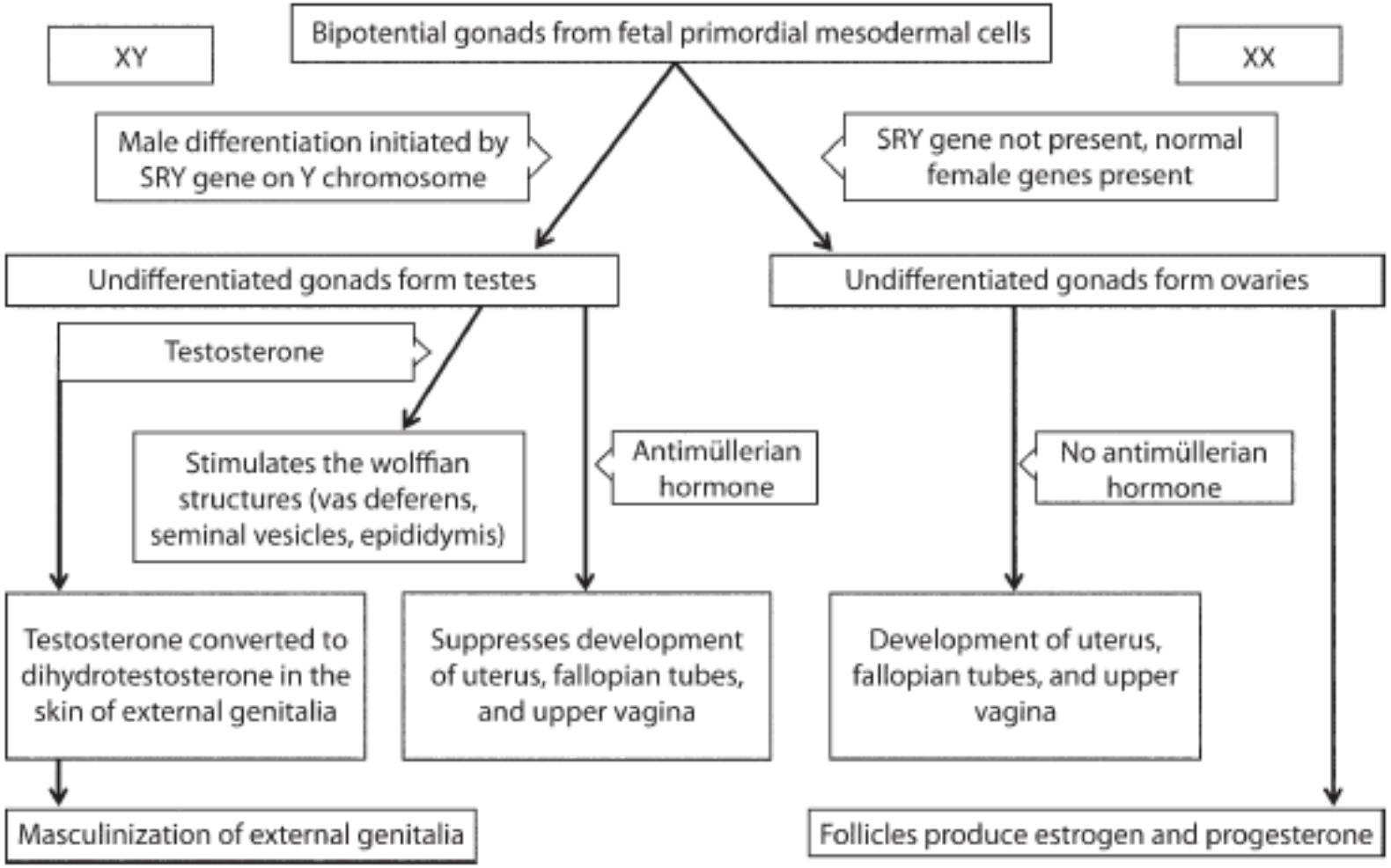


Figure 2. Flowchart shows the hormonal signaling pathways in normal sexual development.

Non-structural causes of DSD

Turner syndrome

- The total complement of chromosomes is 45 in Turner syndrome, which results from a *complete or partial absence of one X chromosome (45XO)*.
- Turner syndrome is the most common chromosomal anomaly in females, occurring in 1 in 2,500 live female births.
- A mosaic karyotype is not uncommon, leading to a variable presentation.

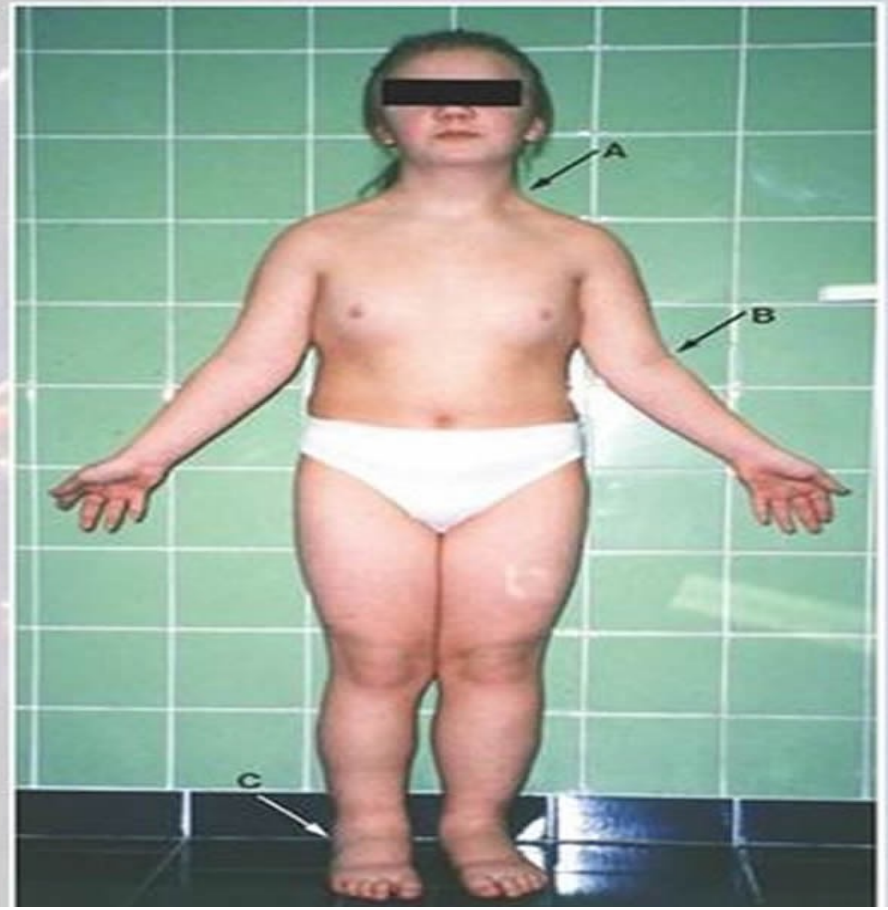
Non-structural causes of DSD

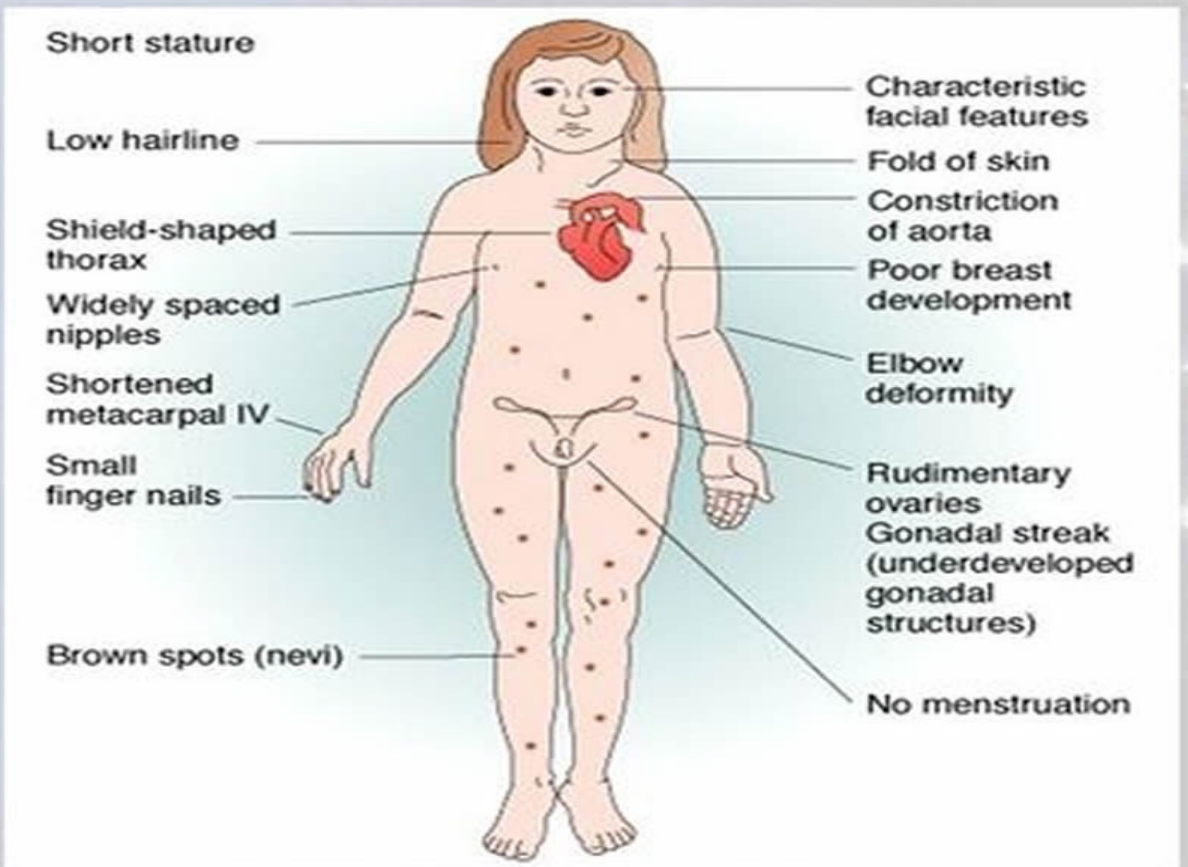
Turner syndrome

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

Turner's Syndrome (X-)

- Missing an X chromosome on 23rd Pair.





Non-structural causes of DSD

Turner syndrome

- 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 estrogen 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% of women, the diagnosis is not made until adolescence with delayed puberty.

Non-structural causes of DSD

Turner syndrome

- **The ovaries do not produce estrogen, so the normal physical changes of puberty cannot happen.**
- **Treatment; In childhood, is focused on growth, but in adolescence it focuses on induction of puberty.**
- **Pregnancy is only possible with ovum donation.**
- **Psychological input and support is important. In girls with mosaicism the clinical picture can vary and normal puberty and menstruation can occur, with early cessation of periods.**

46XY gonadal dysgenesis

- In this situation, the gonads do not develop into a testis, despite the presence of an XY karyotype. In about 15% of cases, this is *due to a mutation in the SRY gene on the Y chromosome,* 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 anti-Müllerian hormone (AMH), the Müllerian structures do not regress and the uterus, vagina and Fallopian tubes develop normally.

46XY gonadal dysgenesis/Swyer syndrome

- The absence of testosterone means the fetus does not virilize. The baby is phenotypically female, although has an XY chromosome.
- The gonads do not function and presentation is usually at adolescence with delayed puberty.
- The dysgenetic gonad has a high malignancy risk and should be removed when the diagnosis is made. This is usually performed laparoscopically.
- Puberty must be induced with estrogen and pregnancies have been reported with a donor oocyte.
- Full disclosure of the diagnosis including the XY karytoype is essential, although this can be devastating and specialized psychological input is crucial.

46XY gonadal dysgenesis/ mixed

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

XY female:Gonadal dysgenesis 8

disorder	genetics	Genetalia	Gonads	featurs	hormones
Pure gonadal dysgenesis Swyer synd	SRY ZFY, SOX9, SF1, WT1, DYZ1, and DAX1	Female Mullerian	Dysgenetic/ streak ovotestes or UD		Low basal and stim Androgens ,AMH ,high LH
Partial gonadal (testicular) dysgenesis		From clitoromegaly, to amb genitalia or hypospadias. +/-Mullerian or mixed	B/L dysgenetic testes	mild clitoromegaly pubertal androgenization .	less severe
Mixed		mullarian	One streak and one dysgenetic or n		

46XY DSD/AIS

- The most common cause of 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 Müllerian ducts. Hence, CAIS women do not have a uterus.

46XY DSD/AIS

- 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.
- The baby is born with *normal female external genitalia*, an absent uterus and with testes that are found somewhere in their line of descent through the abdomen from the pelvis to the inguinal canal.

46XY DSD/ AIS

- Presentation is usually at puberty with primary amenorrhea, although if the testes are in the inguinal canal they can cause a hernia in a younger girl.
- Once the diagnosis is made, initial management is psychological with full disclosure of the XY karyotype and the information that the patient will be infertile.
- Gonadectomy once diagnosed to avoid malignant transformation. ERT should be initiated following gonadectomy. The patient is sterile (no uterus, no ovaries).
- Vaginal repeated dilation or a vaginal reconstruction operation for lengthening.

46XY DSD/AIS

- In cases of partial androgen insensitivity (PAIS), the androgen receptor can respond to some extent with limited virilization.
- The child is usually diagnosed at birth with ambiguous genitalia.

46XY DSD:
5-Alpha-reductase deficiency

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

46XY DSD:
5-Alpha-reductase deficiency

- 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 (*HETEROSEXUAL 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.

46XX DSD

- The most common cause of 46XX DSD, congenital adrenal hyperplasia (CAH), 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% 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.

46XX DSD

- 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 external 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-hydroxylase CAH will have a 'salt-losing' variety, which also affects the ability to produce aldosterone.

46XX DSD

- This represents a life- threatening situation, and those children who are salt-losing often become dangerously unwell within a few days of birth.
- Affected individuals require life-long 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.

46XX DSD

- **This management** is now controversial as adult patients with CAH are very dis-satisfied 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 (MDT) involving surgeons, endocrinologists and psychologists.

KEY LEARNING POINTS

- The hypothalamus, pituitary, ovary and the end organ endometrium have a subtle interplay.
- Normal puberty and a regular menstrual cycle require function of each organ and healthy hormonal interaction.
- DSD may be diagnosed at birth but some cause delayed puberty or primary amenorrhea.

THANKS

For furthure information about AMENORRHEA you can follow this link:
https://www.slideshare.net/OSAMAWARDA/amenorrheawarda

For detailed information about DSD, you can follow this link:
https://www.slideshare.net/OSAMAWARDA/disorders-of-sex-development-o-warda