PRIMARY AMENORRHEA

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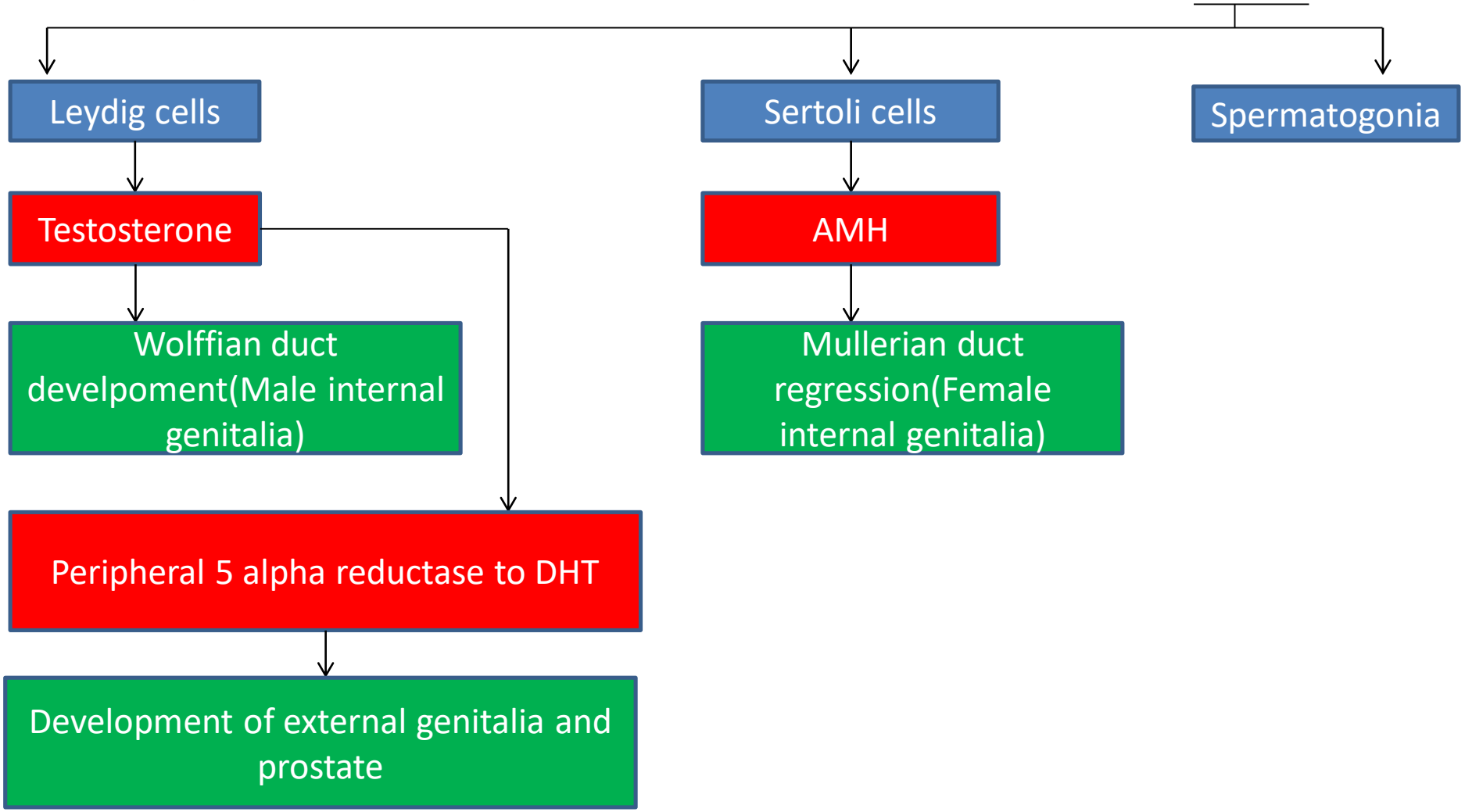
SEXUAL DEVELOPMENT IN UTERO

Embryonic genetic sex (XX or XY) determines **gonadal sex**, the gonads then either produce hormones (if male) OR no hormones (female). The hormonal environment determines the sex of the reproductive tract (**internal and external genitalia**)



IN FEMALE

46 XX : No SRY → Gonads → **Ovaries** (oogonia= primary oocytes and granulosa cells)

No AMH → **Mullerian duct development (female internal genitalia)**
No testosterone → Wolffian duct regression
No DHT → **development of female external genitalia**

Hypothalamic-Pituitary-Ovarian Axis

Hypothalamus

a. Gonadotropin-releasing hormone (GnRH)

Anterior pituitary

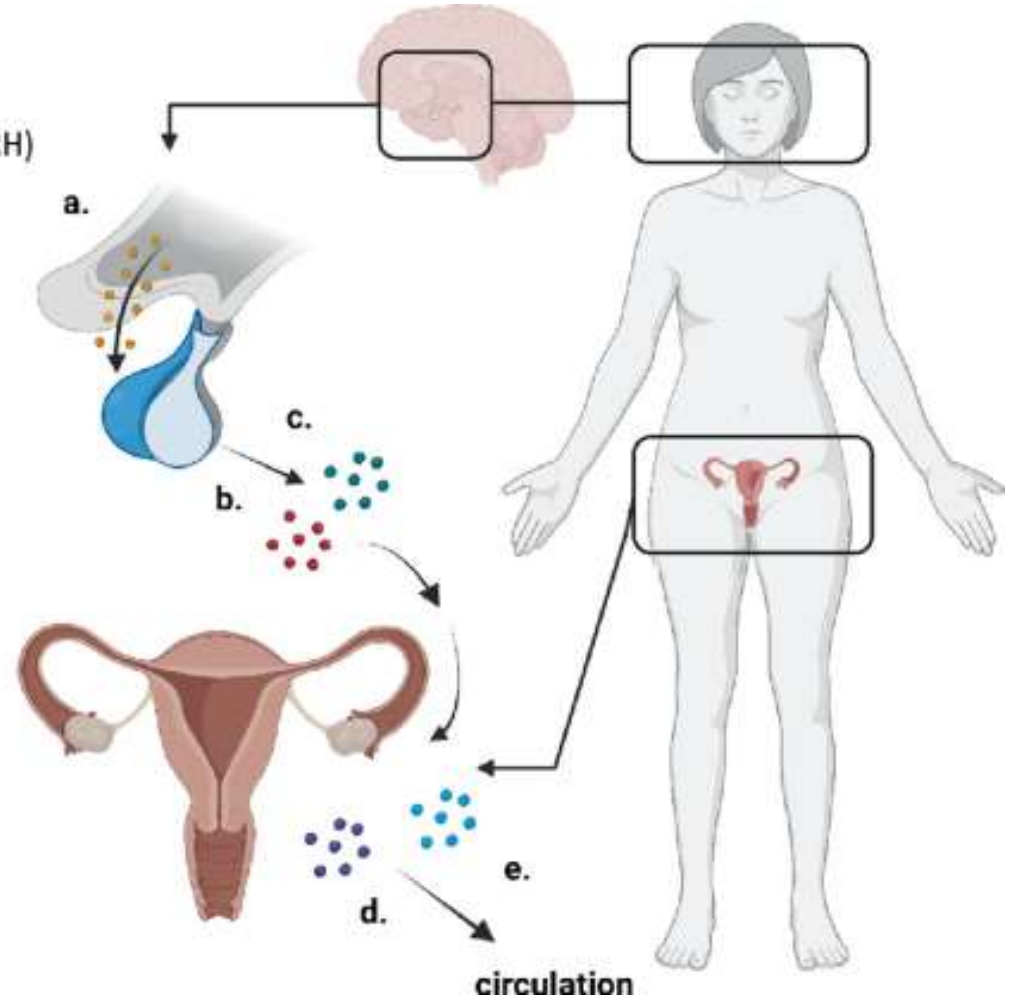
b. Follicle-stimulating hormone (FSH)

c. Luteinizing hormone (LH)

Ovary

d. Estradiol-β-17

e. Progesterone



Primary amenorrhea is defined as the **absence of menses at age 15 years in the presence of normal growth and secondary sexual characteristics.**

- At age 13 years, if no menses have occurred and there is a complete absence of secondary sexual characteristics such as breast development, evaluation for primary amenorrhea should begin.

CAUSES OF PRIMARY AMENORRHEA

Primary amenorrhea is usually the result of a **genetic** or **anatomical** abnormality.

1) Gonadal dysgenesis, including Turner syndrome – 43 %
2) Müllerian agenesis (absence of vagina, sometimes with absence of uterus) – 15 %
3) Physiologic delay of puberty (constitutional delay of puberty)- 14 %
4) Polycystic ovary syndrome (PCOS) – 7 %
5) Isolated gonadotropin-releasing hormone (GnRH) deficiency – 5 %
6) Transverse vaginal septum – 3 %
7) Weight loss/anorexia nervosa – 2 %
8) Hypopituitarism – 2 %
9) Less common etiologies (≤1 % each) included imperforate hymen, complete androgen insensitivity syndrome, hyperprolactinemia/prolactinoma, other pituitary tumors, congenital adrenal hyperplasia, hypothyroidism, central nervous system defects, craniopharyngioma, and Cushing disease.

Hypothalamic and pituitary disease

1) Functional hypothalamic amenorrhea

- It is characterized by abnormal hypothalamic GnRH secretion leading to decreased gonadotropin pulsations, low or normal serum luteinizing hormone (LH) concentrations, absence of normal follicular development, absent LH surges, anovulation, and low serum concentrations of estradiol. Serum follicle-stimulating hormone **(FSH) concentrations are often in the normal range**, with a high FSH-to-LH ratio similar to the pattern in prepubertal females.
- Multiple factors may contribute to the pathogenesis of functional hypothalamic amenorrhea, including eating disorders (such as anorexia nervosa), exercise, and stress.

2) Isolated GnRH deficiency

- These females have prepubertal low serum gonadotropin concentrations due to the absence of hypothalamic GnRH.
- Can be inherited as an autosomal dominant, autosomal recessive, or X-linked condition.
- If it is associated with anosmia, Kallmann syndrome.

3) Constitutional delay of puberty

- Should be a diagnosis of exclusion.
- Characterized by both delayed adrenarche and gonadarche.
- It is often difficult to distinguish clinically from congenital GnRH deficiency.
- More common in males (fivefold).

4) Hyperprolactinemia

- The presentation is similar to hypothalamic amenorrhea except for the additional finding of galactorrhea in some patients, and elevated serum prolactin level.

5) Infiltrative diseases and tumors

Many infiltrative diseases and tumors of the hypothalamus and pituitary can result in diminished GnRH release or gonadotrope destruction and amenorrhea; these include craniopharyngioma, germinoma, and Langerhans cell histiocytosis. The main indications for MRI are hypogonadotropic hypogonadism, visual field defects, headaches, other evidence of hypothalamic or pituitary dysfunction, or symptoms suggestive of other diseases (such as sarcoidosis).

6) Systemic illness

- Can cause secondary or primary amenorrhea when it is severe enough to result in a decrease in hypothalamic GnRH secretion. Examples include celiac disease, type 1 diabetes mellitus, and inflammatory bowel disease.

Gonadal dysgenesis

- The most common cause of primary amenorrhea.
- Caused by chromosomal or genetic abnormalities.
- These disorders result in premature depletion of all ovarian oocytes and follicles(ovarian failure). These individuals have **significantly elevated FSH levels** due to the absence of ovarian oocytes and follicles, leading to reduced negative feedback on FSH from estradiol and inhibin B.
- The largest number of patients have Turner syndrome (45,X as well as other karyotypes), followed by 46,XX gonadal dysgenesis (typically autosomal) and, rarely, 46,XY gonadal dysgenesis.

•Turner syndrome — Females with Turner syndrome are missing all of one X chromosome in 55 to 60 percent of cases (45,X gonadal dysgenesis). Amenorrhea occurs because the oocytes and follicles undergo accelerated apoptosis (in utero in most cases). The ovaries are replaced with fibrous tissue, and in the absence of follicles, there is no ovarian estrogen secretion. In contrast, the external female genitalia, uterus, and fallopian tubes develop normally until puberty when estrogen-induced maturation fails to occur. Spontaneous puberty and menstruation occur more commonly in females with a mosaic karyotype (45,X/46,XX).

Polycystic ovary syndrome

- Rarely cause of primary amenorrhea.
- The females with PCOS who present with primary amenorrhea typically have higher androgen levels and are more overweight.
- The diagnosis can be made in a female with clinical and biochemical evidence of hyperandrogenism in the presence of advanced pubertal development (ie, greater than or equal to Tanner stage 4 breast development) and in the absence of other disorders causing amenorrhea and hyperandrogenism.

Outflow tract disorders

Congenital abnormalities of the female reproductive organs account for approximately 20 % of cases of primary amenorrhea.

1) Imperforate hymen

- It is the simplest defect that results in primary amenorrhea.
- It may be associated with cyclic pelvic pain and a perirectal mass from sequestration of blood in the vagina (hematocolpos).
- Diagnosed by physical examination.
- Is easily corrected with surgery.

2) Transverse vaginal septum

- Can occur at any level between the hymenal ring and the cervix.
- The major symptoms are similar to those associated with an imperforate hymen.
- Surgical resection is needed.

3) Müllerian agenesis

- Also known as vaginal agenesis or Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, refers to congenital absence of the vagina with variable uterine development. It is usually accompanied by cervical and uterine agenesis.
- Can be differentiated from androgen insensitivity based upon a normal, female-range serum total testosterone in vaginal agenesis and a male-range serum testosterone in androgen insensitivity.

Receptor abnormalities and enzyme deficiencies

Complete androgen insensitivity syndrome
5-alpha-reductase deficiency
17-alpha-hydroxylase deficiency
P450 oxidoreductase deficiency
Estrogen resistance

Complete androgen insensitivity syndrome

- Is an X-linked recessive disorder in which 46,XY subjects have a normal female phenotype.
- These patients are **resistant to testosterone** due to a defect in the androgen receptor and, therefore, fail to develop all of the male sexual characteristics that are dependent upon testosterone
- The external genitalia are typically female in appearance,
- Testes may be palpable in the labia or inguinal area.
- The testes make müllerian-inhibiting substance, which is functional and causes regression of all müllerian structures: the fallopian tubes, uterus, and upper third of the vagina
- At puberty, breast development occurs, but the areolae are pale and pubic and axillary hair is sparse.
- The diagnosis of this disorder is based upon the absence of the upper vagina, uterus, and fallopian tubes on physical examination and pelvic ultrasonography; high serum testosterone concentrations (in the range for normal men); and a male (46,XY) karyotype. The testes should be surgically excised after puberty if located intraabdominally because of the increased risk (2 to 5 percent) of developing testicular cancer after age 25 years.

5-alpha-reductase deficiency

- Congenital defect that can result in primary amenorrhea in a 46,XY subject, due to autosomal recessive condition.
- At birth, these neonates may appear female or have ambiguous genitalia due to an inability to convert testosterone (via 5-alpha-reductase) to its more potent metabolite dihydrotestosterone (DHT).
- At puberty, the disorder is more recognizable because of the onset of virilization (male-pattern hair growth, increased muscle mass, and voice deepening) due to the normal peripubertal increase in testosterone secretion in males.

17-alpha-hydroxylase deficiency

This rare disorder, which can occur in 46,XX or 46,XY subjects, is characterized by deficiency of the product of the CYP17 gene, which is an enzyme that has both 17-hydroxylase and 17,20-lyase activities (figure 3). As a result, there is decreased cortisol synthesis but overproduction of corticotropin (ACTH), corticosterone, and deoxycorticosterone. Adrenal and gonadal sex steroids are not produced, so that affected subjects typically present as phenotypic females with hypertension (due to mineralocorticoid excess), lack of pubertal development, and either female (if 46,XX) or incompletely developed (if 46,XY) external genitalia.

EVALUATION

Evaluated by focusing on the presence or absence of breast development (a marker of estrogen action and therefore function of the ovary), the presence or absence of the uterus (as determined by ultrasound, or in more complex cases by magnetic resonance imaging [MRI]), and the follicle-stimulating hormone (FSH) level.

- If the serum FSH concentration is elevated, the probable diagnosis is gonadal dysgenesis and a karyotype should be obtained. The most common karyotypes observed are 45X Turner syndrome
- If FSH is normal and the ultrasound indicates that the uterus is absent, the probable diagnosis is müllerian agenesis or androgen insensitivity syndrome.
- If the FSH is normal, breast development is present, and the ultrasound or MRI detects accumulated blood in the uterus (hematometra) or vagina (hematocolpos), an obstructed outflow tract is present.
- If the FSH is low or normal and the uterus is present, further evaluation is guided by the degree of pubertal development. This could include distinguishing between constitutional delay of puberty and congenital GnRH deficiency, or investigating some of the common causes of secondary amenorrhea that also cause primary amenorrhea.

History

-Has she completed other stages of puberty, including a growth spurt, development of axillary and pubic hair, apocrine sweat glands, and breast development? Lack of pubertal development suggests deficient estradiol secretion, which could be due to a hypothalamic or pituitary disorder, ovarian failure, and/or a chromosomal abnormality.

-Is there a family history of delayed or absent puberty (suggesting a possible familial disorder)?

-What is the woman's height relative to family members? Short stature may indicate Turner syndrome or growth hormone deficiency due to hypothalamic-pituitary disease.

-Were neonatal and childhood health normal? Neonatal crisis suggests congenital adrenal hyperplasia. Alternatively, poor health may be a manifestation of hypothalamic-pituitary disease.

-Are there any symptoms of hyperandrogenism (acne, hirsutism) or virilization? The presence of acne or hirsutism is consistent with a diagnosis of PCOS, while virilization suggests more severe androgen excess, due to an androgen-secreting ovarian or adrenal tumor, or 5-alpha-reductase deficiency.

-Has there been stress; change in weight, diet, or exercise habits; or illness that might result in hypothalamic amenorrhea?

-Is she taking any drugs that might cause or be associated with amenorrhea?

-Does she have galactorrhea, which would suggest excess prolactin? This could be caused by hypothalamic or pituitary disease or by drugs, such as metoclopramide and antipsychotic drugs.

-Are there symptoms of other hypothalamic-pituitary disease, including headaches, visual field defects, fatigue, or polyuria and polydipsia?

Physical examination

- For secondary sexual characteristics, Breast development and pubic hair as assessed by Tanner staging.
- Growth, including height, weight.
- Skin findings such as hirsutism, acne, striae, increased pigmentation, and vitiligo.
- Physical features of Turner syndrome such as low hairline, webbed neck, shield chest, and widely spaced nipples.
- A careful genital examination should be performed for clitoral size, pubic hair development, intactness of the hymen, vagina.

Pelvic ultrasound…….MRI

should be performed to confirm the presence or absence of ovaries, uterus, and cervix. In addition, ultrasonography can be useful to look for vaginal or cervical outlet obstruction in patients with amenorrhea and cyclic pain.

laboratory testing

FSH,LH,ESTRADIOL,TSH,PROLACTIN,TESTOSTERONE

karyotypye

MANAGEMENT

Treatment of primary amenorrhea is directed at correcting the underlying pathology (if possible), helping the woman to achieve fertility (if desired), and prevention of complications of the disease process (eg, estrogen replacement to prevent osteoporosis).