

CAUSES OF AMENORRHEA

Dr. Clisham

Definition:

A. Primary amenorrhea:

(1) No period by age 14 in the absence of growth or development of secondary sexual characteristics.

(2) No period by age 16 regardless of the presence of normal growth and development with the appearance of secondary sexual characteristics.

B. Secondary amenorrhea

In a woman who has been menstruating, the absence of periods for a length of time equivalent to a total of at least three of her previous cycle intervals or six months without a menstrual flow.

C. Can be a transient, intermittent or a permanent condition.

The result of dysfunction of the hypothalamus, pituitary, ovaries, uterus, or vagina.

Formulating a differential diagnosis:

GESTATIONAL CAUSES

Pregnancy – Pregnancy is the most common cause of amenorrhea and should be the first step in evaluating any woman with amenorrhea.

ANATOMIC CAUSES

A. CONGENITAL ABNORMALITIES –

Imperforate hymen – may be associated with cyclic pelvic pain and a peri-rectal mass. Similar findings can be seen with defects in perineal development, which can result in absence of the distal third of the vagina and therefore absence of an outflow tract. Both of these conditions are diagnosed by physical examinations and an imperforate hymen is easily corrected with surgery.

Abnormal Mullerian development – Rokitansky-Kuster-Hauser syndrome - Includes defects of absence of the Mullerian structures (fallopian tubes, uterus, and upper third of vagina), resulting in agenesis or partial agenesis of the uterus and cervix). Absence of these Mullerian structures also occurs in the testicular feminization syndrome and the vanishing testes syndrome (in which an external vaginal opening is usually present).

Testicular feminization syndrome – A 46 XY individual that appears as a normal phenotypic female because of a defect in the androgen receptor. They are resistant to testosterone and fail develop male sexual characteristics. The external genitalia are female in appearance, but testes may be palpable in the labia or inguinal area. The testes function normally, making Mullerian inhibiting substance, causing regression of all Mullerian structures and the absence of fallopian tubes, internal uterus, and upper third of the vagina. They also produce testosterone, which can be converted into estrogens by peripheral conversion in the fat, thus allowing for breast developing. The diagnosis is made from the absence of female genital organs on physical examination and pelvic ultrasonography, elevated serum testosterone levels (in the male range), and a male 46 XY karyotype.

5-alpha-reductase deficiency: In a 46 XY individual, this enzyme deficiency leads to failure of dihydrotestosterone-dependent masculinization (enlargement of the male external genitalia and prostate) in fetal development. 5-alpha-reductase is required to convert testosterone to DHT. DHT is necessary for development of external genitalia. Lack of DHT will lead to a female phenotype. This disorder should be recognizable at puberty because of the onset of virilization due to the normal peripubertal increase in testosterone levels in males. In comparison, testosterone-dependent processes are intact, including male pattern hair growth, muscle mass, and voice deepening.

Vanishing testes syndrome – These patients appear as normal females with a 46XY genotype. The phenotype may be variable depending upon when gonadal failure occurs.

A. Early failure: If failure occurs prior to testicular development (before about eight weeks of gestation), it is associated with streak-like inactive gonads which never produce testosterone, estrogen, or inhibiting substance, causing the individual to feminize internally and externally and present at puberty with gonadal failure.

B. Late failure: If the testicles fail, variable abnormalities can result depending on when the failure occurs. An individual could have normal external genitalia at birth, but fail to exhibit normal pubertal events due to gonadal failure.

C. The diagnosis of the vanishing testes syndrome is made from the findings of ovarian failure, lack of progression through puberty, and elevated gonadotropin levels (FSH and LH) in the presence of a male karyotype.

D. Testis Determine Factor Gene deletion: These 46 XY individuals do not develop testes and therefore do not produce testosterone or Mullerian inhibiting substance, resulting in

feminization of the external and internal genitalia in association with primary gonadal failure due to a deletion in the TDF gene.

B. ACQUIRED ANATOMIC LESIONS –

Asherman's syndrome: a cause of secondary amenorrhea. Associated with a history of uterine instrumentation (especially dilatation and curettage), uterine infection, or obstetrical complication. The diagnosis is suggested by the absence of a normal uterine stripe on pelvic ultrasound and can be confirmed by the absence of withdrawal bleeding after a test course of estrogen and progestin replacement.

ENDOCRINE

A. OVARIAN DISORDERS – The major ovarian causes of amenorrhea are hyperandrogenism, from internal or external sources, and ovarian failure due to normal or early menopause.

Hyperandrogenism – Hyper-androgenism is a common disorder accounting for approximately 20 percent of cases of amenorrhea. The excess androgens can come from adrenal, ovarian, or exogenous sources. Increased androgens from any source cause amenorrhea by two mechanisms:

Androgens interfere with normal follicular development and ovulation altering the normal hormonal profile of the menstrual cycle. Androgens are converted to estrogens by aromatase activity in the peripheral fat, however, the failure to develop a follicle and the subsequent corpus luteum at ovulation eliminates progesterone production and eventual withdrawal bleeding when the corpus luteum regresses. High levels of Androgen may cause endometrial atrophy.

Polycystic Ovarian Syndrome (PCOS) is a clinical diagnosis classically defined by hirsutism (hyperandrogenism), obesity and annovulation. The minimal criteria for the diagnosis of PCOS are hyperandrogenism and oligomenorrhea or amenorrhea. Hyperandrogenism is usually manifested clinically as acne and/or hirsutism and chemically as an elevation in the serum concentration of at least one androgen (testosterone, androstenedione, DHEAS)

PCOS is a diagnosis of exclusion. Important distinguishing features are its peripubertal onset and worsening with weight gain. Thin women are not excluded from having this disorder. In older women, other diagnoses should be considered in older women with a sudden change in cycles or increased hair growth.

The minimal evaluation for suspected PCOS include measurement of the serum concentrations of prolactin (to rule out hyperprolactinemia) and testosterone (a value below 200 ng/mL excludes an androgen-secreting adrenal tumor). Pelvic ultrasonography may show multiple small ovarian cysts (string of pearls) in the periphery of the ovary with increased ovarian stroma.

PCOS patients also have elevated mean serum LH levels, as well as increased LH pulse frequency and amplitude. FSH levels may be normal or low, leading to an LH to FSH ratio above normal in approximately 90 percent of women with PCOS. The cause of the gonadotropin abnormality is not known, but it can be used to help distinguish PCOS from hypothalamic amenorrhea which is typically associated with a low LH to FSH ratio.

Ovarian failure – results from the lack of oocytes. This may occur in five percent of women under the age of 40 resulting in amenorrhea. This syndrome is called premature menopause or premature ovarian failure.

Examining gonadotropin values will provide an important marker to distinguish hypothalamic and pituitary cause of amenorrhea from those resulting from ovarian failure.

Causes of Premature Ovarian Failure:

Idiopathic

autoimmune

polyglandular autoimmune syndrome (type 1 and 2)

anti-thyroid antibodies

anti-adrenal antibodies

karyotypic abnormalities

radiation or chemotherapy

Turner's syndrome – 45X,O karyotype

Classic abnormalities

Lymphedema at birth

Short stature

Webbed neck

Low posterior hairline

low set ears

widely spaced nipples

cardiac disorders

Later abnormalities: Hearing loss, hypertension, hypothyroidism, and liver function abnormalities.

B. HYPOTHALAMIC AND PITUITARY DISEASE –

Functional hypothalamic amenorrhea. Dysfunction secondary to tumors and /or infiltrative lesions which are usually associated with hyperprolactinemia.

Hypothalamic amenorrhea –a functional disorder which is characterized by abnormal gonadotropin-releasing hormone (GnRH) regulation, decreased gonadotropin pulsations, absent LH surges, anovulation, and low serum estradiol. FSH release tends to be normal.

Factors contributing to HA-

- A) Weight
- B) Exercise
- C) Nonspecific stresses (emotional, illness)
- D) GnRH deficiency - idiopathic hypogonadotropic hypogonadism - Kallman's syndrome (anosmia)

Hyperprolactinemia –

- a. second major cause of functional HA
- b. additional finding of galactorrhea in 50 to 80 percent of women
- c. a serum prolactin level should be measured in every woman with amenorrhea
- d. repeat serum prolactin level before cranial imaging
- e. Primary cause: prolactinoma
- f. Other causes: stalk compression
empty sella syndrome
hypothyroidism

Women with amenorrhea secondary to hyperprolactinemia typically have rapid resumption of menses and fertility once prolactin levels are normalized as with bromocriptine for prolactinoma.

Other hypothalamic and pituitary lesions –

- a. Infiltrative diseases: result in diminished GnRH release, low or normal serum gonadotropin levels
 - i. Histiocytosis X
 - ii. Gumma
- b. Hemochromatosis: hemosiderin toxicity for the gonadotrope
- c. Tumors:
 - i. Craniopharyngioma
 - ii. Meningiomas
 - iii. Gliomas
 - iv. Metastatic tumors
 - v. Chordomas
- d. Sheehan's Syndrome