Primary Amenorrhea

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Amenorrhea is the absence or abnormal stopping of menstruation.[1] It is termed primary or secondary depending on whether menstruation stopped before or after menarche.

When should the evaluation be started? [2]

- No menstruation by the age of 15 but has well developed secondary sexual characters.
- Breast development has started before age 10 but has not menstruated 5 years after that.
- No evidence of breast development even at 13 years of age.

Incidence:

Abnormalities of development contribute to 60% of causes for primary amenorrhea and 40% are due to endocrine causes. [3]

Work up:

Pregnancy should be ruled out and clinical features should be taken into consideration. Evaluation is needed to check whether there is a functioning hypothalamo-pituitary axis with a normal utero-vaginal anatomy.

Evaluation:

A detailed history is obtained and the girl is examined for stature, body mass index (BMI) and habitus. Development of secondary sexual characters and external genitalia development is ascertained. The girl is examined in the presence of her mother. [3]

Delay in development of secondary sexual characters:

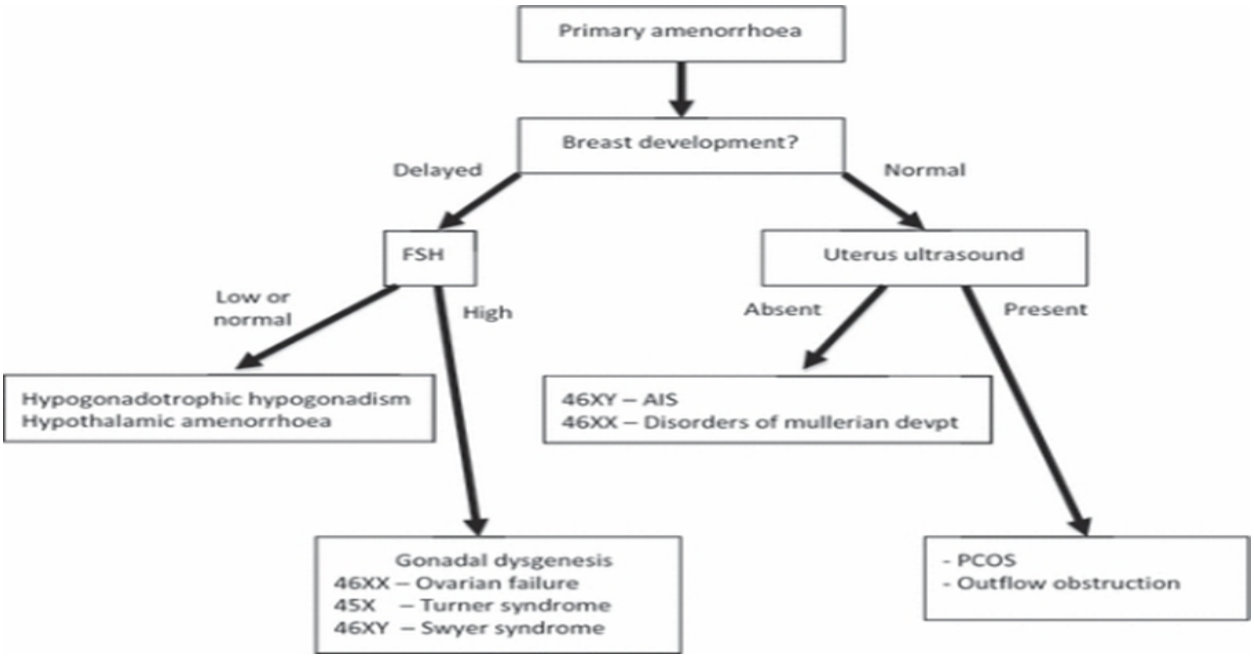
If the girl has delayed breast development, follicular stimulating hormone (FSH) is estimated. Normal levels of FSH are between 5-20 IU/L.

If it is very high and above 40 IU/L, it indicates ovarian failure. [3] The gonadal cause can be gonadal dysgenesis and a karyotyping is essential. It may be 46XX ovarian failure; 45XO Turner's syndrome or 46 XY Swyer syndrome.

If the FSH level is abnormally low, it indicates a problem at the hypothalamus or pituitary. It is hypogonadotropic hypogonadism. If the BMI is low, an eating disorder or abnormal physical activity is ruled out. The other causes are hyperprolactinemia or an intra cranial tumor. Serum prolactin estimation and imaging studies of the brain are done when necessary.

Normal development of secondary sexual characters:

An abdominal ultrasound is done to identify the uterus and the ovaries. If uterus is absent, a karyotyping is done to differentiate between 46XY androgen insensitivity syndrome and 46XX Mullerian abnormalities. If the uterus is present, an outflow tract obstruction is ruled out. If the girl has hyperandrogenic features with a normal uterus, polycystic ovarian syndrome is ruled out.



Commonest causes of primary amenorrhea

- Gonadal dysgenesis
- Mullerian agenesis
- Androgen insensitivity syndrome

Correlation between pubertal changes for evaluation:

- Sexual infantilism with short stature: hallmark of gonadal dysgenesis
- Breast development: reliable indicator of endogenous estrogen production or exposure to exogenous estrogen
- Pubic hair growth: reflects androgen production and exposure
- There should be symmetry between breast development and pubic hair growth. Their Tanner stages should be consistent
- Scanty pubic hair with advanced breast development is classic of androgen insensitivity syndrome

Immature secondary sexual characters indicate low levels of FSH.

- If FSH is high, it indicates gonadal dysgenesis
- If FSH is low, it indicates chronic anovulation due to PCOS, pituitary or hypothalamic cause

High FSH-Gonadal dysgenesis

Commonest cause is Turner's syndrome

- Classical is 45X karyotype
- Can have other structural abnormalities of X chromosome
- Short stature, absent sexual development, webbed neck, low set ears and posterior hairline, widely spaced nipples, short 4th metacarpals and cubitus valgus can be present.
- Mosaicism can occur. 45X/46XX cell line can have some degree of sexual development. May have secondary amenorrhea.

Swyer syndrome- 46XY Gonadal dysgenesis

- In spite of the presence of Y chromosome, there are streak gonads which do not secrete androgens or AMH.
- Hence “default” female phenotype
- The vagina, cervix, uterus and fallopian tubes develop
- Normal adrenarche is seen
- Karyotyping is conclusive
- Can achieve pregnancy with donor egg IVF

Mature secondary sexual characters with normal growth

- If patent vagina and presence of cervix, rule out

- Mullerian/ vaginal agenesis
- AIS
- Obstructive causes like imperforate hymen and transverse vaginal septum

Androgen insensitivity syndrome (AIS): The following characteristics may be present:

- Normal male karyotype 46XY
- Testes are the gonads that produce testosterone and anti-mullerian hormone (AMH)
- Gene mutation in the gene encoding for the androgen receptors in long arm of X chromosome results in end organ insensitivity to androgen actions
- No peripheral androgen actions- default female external genitalia
- AMH signaling is intact- hence male internal genitalia with regression of Mullerian structures
- Phenotypic females with absent cervix and uterus and blind vagina derived from urogenital sinus
- Tall individuals

Conclusion:

Many of the conditions that contribute to primary amenorrhea may be diagnosed early in infancy or childhood. At whatever age the child presents, a thorough evaluation is done as a multidisciplinary approach. This is necessary to avoid social and health issues in adulthood.

References:

1.Practice Committee of the American Society for Reproductive Medicine ;Fertil Steril. 2006;86(5 Suppl 1):S148.

2.Herman-Giddens ME, Slora EJ, Wasserman RC, Bourdony CJ, Bhapkar MV, Koch GG, Hasemeier CM. Secondary sexual characteristics and menses in young girls seen in office practice: a study from the Pediatric Research in Office Settings network. Pediatrics. 1997 Apr 1;99(4):505-12.

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