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Physiology, Menarche

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Introduction

Menarche is defined as the first menstrual period in a female adolescent. Menarche typically occurs between the ages of 10 and 16, with the average age of onset being 12.4 years.[1] The determinants of menarcheal age are continuously being researched; socioeconomic conditions, genetics, general health, nutritional status, exercise, seasonality, and family size are thought to play a role.

Menarche tends to be painless and occurs without warning. The first cycles are usually anovulatory with varied lengths and flow. Menarche signals the beginning of reproductive abilities and is closely associated with the ongoing development of secondary sexual characteristics.[2]

Issues of Concern

Menarche occurs in the setting of a maturing hypothalamic-pituitary-ovarian (HPO) axis and relies on the following processes: normal hypothalamic and pituitary function, normal female reproductive anatomy, normal nutrition, and the general absence of other intervening chronic illnesses. It is a marker of normal female reproductive health and wellness. Most females recognize menarche as their body's critical declaration of fertility.

The absence of normal menstrual periods, unrelated to pregnancy, is termed amenorrhea. Primary amenorrhea is the complete absence of menstruation by 15 years of age in the setting of normal growth and secondary sexual development or the absence of menses by age 13 in the absence of normal growth or secondary sexual development. Secondary amenorrhea is the absence of menses for greater than three cycle intervals or six consecutive months in a previously menstruating female.[3]

Of specific concern is when menarche occurs too early, too late, or not at all, as these scenarios have future adverse outcomes. Menarche is considered early if it occurs at or before ten years of age and late if it occurs at or later than 15 years of age.[4]

Cellular Level

Numerous studies have shown the kiss1 gene, which produces kisspeptin, and its receptor G protein-coupled receptor 54 (GPR54) to be necessary for normal reproductive function. Kisspeptin and GPR54 are expressed in hypothalamic gonadotropin-releasing hormone (GnRH) neurons. The hypothalamic kiss1 system relays metabolic information to the gonadotropic axis. Circulating estradiol activates kisspeptin, which in turn activates GnRH neurons. Puberty is initiated when GnRH is secreted in a pulsatile manner by hypothalamic neurons.[5]

A single nucleotide polymorphism on chromosome 6, LIN28B, has been found to be associated with earlier menarche.[6]

Development

GnRH neurons are found in the olfactory pit at post-conception week six, then migrate via the forebrain to the hypothalamus by week nine. The pituitary begins to secrete luteinizing hormone (LH) and follicle-stimulating

hormone (FSH) into the fetal circulation by week 12, with LH and FSH reaching peak levels at midgestation, around 20-24 weeks. LH and FSH levels are low at birth but begin to increase upon withdrawal of placental estrogens.[7] As previously discussed, the pulsatile release of GnRH, and thus, LH and FSH, is necessary for puberty and menarche. The onset of female puberty is marked by thelarche (breast budding), which typically occurs after eight years of age. Thelarche is followed by pubarche (pubic hair development), growth spurt, and finally, menarche.

Menarche occurs 2-3 years after thelarche and six months after peak height velocity (PHV) is achieved. PHV is defined as the highest velocity observed during the pubertal growth spurt.[8] Menarche most commonly occurs in sexual maturity rating (SMR) or Tanner stage IV. It is abnormal for menarche to occur before the appearance of secondary sexual development. Sexual abuse, genital trauma, tumors, or bleeding disorders should be considered in the differential diagnosis of prepubertal females who experience vaginal bleeding.

By 15 years of age, approximately 98% of females will have undergone menarche, signaling the maturation of the adolescent female body. Menarche is commonly associated with the ability to ovulate and reproduce; the onset of menarche does not guarantee either ovulation or fertility. Menstrual cycles are frequently irregular during adolescence, particularly during the interval from the first to the second cycle.[9] Immaturity of the HPO axis during the early years after menarche results in anovulation and irregular cycles, which can range from short cycles (< 20 days) to long cycles (> 45 days). By the third year after menarche, 60-80% of menstrual cycles are 21 to 34 days long, typical of an adult cycle. In females who undergo early menarche, 50% of their cycles are ovulatory in the first year, and nearly all are ovulatory by the fifth year post-menarche. In contrast, it takes approximately 8 to 12 years for all cycles to be ovulatory in females who experience a later onset of menarche.[10]

Menarche is considered early if it occurs at or before ten years of age and late if it occurs at or later than 15 years of age.[4] Menarche is also considered delayed if there is more than a three-year lapse between the onset of thelarche and the first menses.

The age at which a female experiences menarche is variable, with both genetic and environmental factors such as socioeconomic status, family life, ethnicity, exercise, and dietary factors involved. Several studies have shown there to be an ethnic-racial difference in menarche onset. In one study, Black females experienced menarche three months earlier than White females. This finding may reflect genetic factors, as Black females presented with higher insulin responses to glucose challenges and increased free IGF-1, which are associated with skeletal and sexual maturation.[11]

Organ Systems Involved

In addition to the female reproductive organs (ovaries, fallopian tubes, uterus, and vagina), menarche is influenced by complex hormonal interactions involving the hypothalamus, pituitary gland, and ovaries. The adrenal glands, thyroid, and pancreas have also been shown to play a role in menarche. Thyroid hormones are necessary for normal menses, and their deficiency or excess can inhibit menarche or lead to abnormalities in existing menstrual patterns. Abnormally elevated insulin or adrenal androgens can affect normal ovarian estrogen production and decrease pituitary production of LH. The hormone leptin also appears to play a role in maintaining normal menstrual cycles.[12]

Function

Menarche is an indicator of the onset of fertility and reproductive ability, and its absence should signal the provider to evaluate for pathology.

Menstruation is the monthly shedding of the functional layer of the uterine endometrial lining that occurs when ovulation is not followed by fertilization. It occurs approximately every 28 days, ranging from every 21 to 45 days, with a mean cycle interval of 32.2 days in the first gynecologic year. Most menstrual periods last between three and seven days, with menses lasting more than ten days considered abnormal.[13]

Mechanism

Puberty is initiated when GnRH is secreted in a pulsatile manner by hypothalamic neurons. This pulsatile release of GnRH allows pituitary gonadotrophs to release LH and FSH. LH begins androstenedione production in ovarian theca

cells, while FSH allows aromatase in follicular cells to synthesize estradiol. Increased serum estradiol allows breast tissue to enlarge and influences linear bone growth and epiphyseal fusion, playing a significant role in the pubertal growth spurt.

One year before breast budding, higher peaks of LH are seen exclusively during sleep, caused by an increasing pulse amplitude of GnRH release. When breast budding occurs, LH peak amplitude increases 10-fold and FSH pulse amplitude doubles. Progression of puberty from Tanner stage II to III is marked by a further increase in LH pulse amplitude, a 20 to 40-fold increase from prepubertal levels, reflecting the rise of estradiol levels, which have now become detectable at all hours. Upon reaching Tanner stage IV, LH, and FSH pulses become diurnal and gradually mature to the adult pulsation pattern.[14]

Menarche occurs near the end of Tanner stage IV after a year-long rise in daily estradiol output. High estradiol levels at this time exert negative feedback on the gonadotropic axis to suppress it, leading to cyclic estrogen levels and uterine bleeding.[15] At the time of menarche, positive estradiol feedback on the axis is not yet established; ovulation rarely occurs. Uterine bleeding occurs with varying cyclicity until the mechanism of estrogen-induced LH surge is mature and ovulatory cycles occur. This process generally takes a year or more after menarche to become fully established.

Related Testing

In patients with normal anatomy and delayed development, evaluating ovarian and pituitary hormones, including androgens, can assist in a diagnosis. Pituitary tumors, most often adenomas, can be associated with elevated prolactin levels and physical findings such as galactorrhea, headaches, visual changes, and amenorrhea. In primary amenorrhea, estradiol levels help measure ovarian function. If estradiol levels are low, reflexive testing of FSH and LH will differentiate between primary ovarian insufficiency (FSH/LH elevated) and secondary ovarian insufficiency (FSH/LH low or unmeasurable; pituitary insufficiency).[16]

If physical examination reveals evidence of hirsutism or acne, testing androgen levels, including free and total testosterone, DHEA-S, and 17-hydroxyprogesterone, can help rule out androgen-secreting tumors and congenital adrenal hyperplasia as a cause. Androgen levels may also be used to rule out or confirm a diagnosis of polycystic ovary syndrome (PCOS). It should be noted that the absence of menarche can also occur due to pregnancy, and ruling out pregnancy is essential in the evaluation.

Pathophysiology

Early Menarche

- **Causes**
    - Earlier onset of menarche was seen in those surrounded by stressful family environments, those in foster care, and those living with a stepparent. This is explained through differing lifestyle and psychological factors. Additionally, those raised in urban environments experience menarche at an earlier age when compared to those raised in rural settings.[17]
    - Adolescents from families of high socioeconomic status (SES) experience menarche at an earlier age when compared to those from families of a lower SES.[18]
    - Studies have shown that those who consumed more animal protein and less vegetable protein between the ages of three to five experienced earlier menarche.[19]
    - Multiple studies have shown that having an overweight or obese BMI is a risk factor for early menarche. One such study stated that those with early menarche were 1.7 times more likely to have an overweight or obese BMI.[20] Another study found a positive correlation between the consumption of sugar-sweetened beverages and the onset of menarche. It was reported that consumption of more than 1.5 sugar-sweetened beverages per day experienced menarche approximately 2.7 months earlier than those who consumed less than two sugar-sweetened beverages per week.[21]

- Formula feeding during early infancy has also been researched as a potential factor for early menarche.[22]

- **Outcomes**

  - Early menarche has been associated with physical and psychosocial problems, including anxiety and depression, earlier sexual intercourse, substance use, and suicidal behavior. These outcomes may be attributed to adolescents associating negative physical and psychological changes with menstruation reflecting misconception, ignorance, and the fear of being different from peers.[23]
  - Substantial evidence from multiple countries suggests that females who undergo early menarche are more vulnerable to early pregnancy, sexually transmitted infections, and sexual violence.[24]
  - Early menarche can lead to premature fusion of the epiphyseal growth plates and a final adult height shorter than the potential genetic height.[25]
  - Undergoing menarche at an early age leads to an increased prevalence of hypercholesterolemia in adulthood, increasing the risk of developing cardiovascular diseases such as hypertension, coronary heart disease, and stroke. Studies have also shown an increased risk of developing metabolic syndrome and type 2 diabetes mellitus.[22]
  - Higher bone mineral density of the lumbar spine and femoral neck in older age has been seen in females who underwent early menarche, explained by the prolonged lifetime exposure to the protective effects of endogenous estrogens.[26]
  - Studies have demonstrated a 23% higher risk of developing breast cancer in patients with early menarche when compared with patients who experience delayed menstruation. This finding is enhanced by the observation that early menarche is accompanied by abdominal-type obesity and, thus, higher circulating levels of insulin, testosterone, and insulin-like growth factor 1, which act as growth factors for mammary tissue proliferation and are likely to promote mammary gland carcinogenesis.[27]

Late Menarche

Primary amenorrhea is the term used to describe the absence of menses by age 15 in the setting of normal growth and secondary sexual development or the absence of menses by age 13 in the absence of normal growth or secondary sexual development.

- **Causes**

  - Menarche can be delayed in adolescents with very low body mass due to starvation, malabsorption, or an eating disorder such as anorexia nervosa. It is estimated that minimum body fat of 17% is necessary for menarche, with 22% body fat required for maintaining regular menses.[28]
  - Menarche, on average, occurs later in athletes than in the general population, suggesting that intense exercise of at least two hours per day delays puberty and, therefore, menarche.[29]
  - Additional studies have shown that the presence of older sisters in the household is associated with a later onset of menarche.[30]
  - Menarche can be delayed in normally developing females due to abnormalities of the female genitourinary tract. Females with an imperforate hymen may present with delayed menarche and often have a history of recurrent cyclic abdominal or pelvic pain. These patients may present with a palpable lower abdominal mass and often have a bulging, bluish-colored hymen.[31]
  - The absence of a normal uterus or vagina due to Müllerian agenesis, or Mayer-Rokitansky-Kuster-Hauser syndrome, has an incidence of approximately 1/4500 females and often goes undiagnosed until a patient presents with primary amenorrhea. Other complex hormonal abnormalities, such as androgen insensitivity syndrome, can present with external female development and primary amenorrhea.

Abnormal development of female gonads due to Turner syndrome also can lead to ovarian agenesis and absent menses.[32]

- **Outcomes**
  - Delayed menarche has been shown to decrease mineral density in the forearm, spine, and proximal femur, resulting in osteoporosis and an increased risk of fractures later in life.[33]
  - Late menarche may be positively associated with the risk of developing Alzheimer disease.[2]

Clinical Significance

While there is a set window during which menarche should begin, there is variation within that window with many causes. As previously discussed, socioeconomic status, diet, activity, and genetics can play a role in the initiation of puberty and menarche.

It is crucial to educate prepubertal patients and their guardians on the progression of puberty and the development of the menstrual cycle. It is essential to talk openly about the subject and dispel any fears or misinformation the child may have. Clinicians should convey that females will begin to menstruate approximately 2 to 3 years after breast development begins and that menstruation is a normal part of development. Patients should be instructed on using feminine products and what is considered normal menstrual flow. This should be a collaborative educational effort between the patient, guardian, and clinician.

Several menstrual abnormalities require further evaluation.[34] These include:

- Absence of menarche within three years of thelarche
- Absence of menarche by 14 years of age with signs of hirsutism
- Absence of menarche by 14 years of age with a history or physical examination suggestive of excessive exercise or eating disorder
- Absence of menarche by 15 years of age in the presence of normal growth and development

Anatomical problems leading to amenorrhea can typically be diagnosed by a thorough history, a careful visual exam of the external genitalia, and a manual exam of the reproductive organs of the adolescent female patient. Clinicians should take a history in private and maintain confidentiality whenever possible. It is also essential to explain the physical examination in detail; chaperones should be provided.

Clinically, it is essential to know that both sexual abuse and childhood physical abuse can trigger early menarche. Screening for sexual abuse is a crucial aspect of general practice, but many providers lack a consistent approach to patient evaluation. Menarche may provide clinicians with an opportunity to discuss the topic of sexual initiation and screen for past abuse. As a healthcare provider, noting the presence of early menarche in combination with other physical or behavioral signs and symptoms should prompt a more detailed history.[35]

Review Questions

- Access free multiple choice questions on this topic.
- Comment on this article.

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