The normal menstrual cycle

Khalida Itriyeva, MD

The normal ovulatory menstrual cycle requires the presence of a mature hypothalamic-pituitary-ovarian axis and highly coordinated hormonal feedback loops. Consisting of three phases (follicular, ovulatory, and luteal), the normal menstrual cycle results in the formation of a mature follicle and release of an oocyte during each cycle, with menses occurring in the absence of fertilization. While adolescents may initially experience anovulatory cycles following menarche, the vast majority of cycles will be fairly regular, lasting 21 to 45 days in length with an average of three to seven days of bleeding. Absence of menarche by age 15, absence of menses for three consecutive months, and menses lasting eight days or longer with or without associated heavy bleeding are among the menstrual abnormalities that warrant further evaluation. Obtaining the menstrual history in adolescents with the knowledge of expected menstrual patterns allows the pediatric practitioner to provide appropriate counseling and education to adolescents and their families, and to identify menstrual abnormalities when they arise. Treating the menstrual cycle as a "vital sign" highlights the importance of normal menses as an indicator of an individual's overall health and enables timely identification of any concerning findings.

Curr Probl Pediatr Adolesc Health Care 2022; 52:101183

Introduction

The normal menstrual cycle is the result of a highly coordinated hypothalamic-pituitary-ovarian (HPO) axis with complex hormonal feedback loops that lead to the formation of a dominant follicle, ovulation and, in the absence of fertilization, shedding of the endometrial lining at regular intervals. A fundamental understanding of normal menstrual physiology and normal menstrual patterns in adolescents is vital to providing appropriate counseling, education, and reassurance to patients and families, and for identifying abnormalities when they arise to provide timely referral for evaluation and treatment. This chapter will lay the foundation for the subsequent chapters on menstrual concerns in adolescents by reviewing normal menstrual physiology, the components of a menstrual history, and the characteristics of normal menstrual cycles in adolescents.

The normal ovulatory menstrual cycle consists of three phases: the follicular (proliferative) phase, the ovulatory phase, and the luteal (secretory) phase. Estradiol is the primary hormone of the follicular phase, while progesterone is the primary hormone of the luteal phase.

Normal menstrual physiology

Normal ovulation and menstruation occur as a result of the pulsatile release of gonadotropin-releasing hormone (GnRH) from the hypothalamus, which stimulates the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) by the anterior pituitary. LH and FSH act directly on ovarian cells, resulting in the production of ovarian androgens and estradiol; FSH is additionally responsible for the recruitment of ovarian follicles and follicular growth. Highly coordinated feedback loops result in growth of the endometrial lining and the development of a dominant follicle during the first phase of the menstrual cycle, ovulation mid-cycle, and preparation of the endometrium for implantation in the third phase of the menstrual cycle. Disruptions to any step of the carefully orchestrated process, and abnormalities at any level of the HPO axis, can lead to menstrual disorders, including irregular, infrequent or absent menses, and heavy menstrual bleeding.

The normal ovulatory menstrual cycle consists of three phases: the follicular (proliferative) phase, the

From the Division of Adolescent Medicine, Cohen Children's Medical Center, Northwell Health, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, 410 Lakeville Road, Suite 108, New Hyde Park, Hempstead, NY 11042, USA.

E-mail: kitriyeva@northwell.edu

Curr Probl Pediatr Adolesc Health Care 2022;52:101183
1538-5442/$ - see front matter

https://doi.org/10.1016/j.cppeds.2022.101183

ovulatory phase, and the luteal (secretory) phase. Estradiol is the primary hormone of the follicular phase, while progesterone is the primary hormone of the luteal phase. The follicular phase of the menstrual cycle begins with the onset of menses and ends with ovulation. It is the main determinant of an individual's cycle length, ranging in duration from 7 to 22 days, with an average of 14 days.[1] During the early follicular phase, low levels of estradiol and progesterone stimulate the release of GnRH from the hypothalamus, resulting in secretion of LH and FSH from the anterior pituitary. The presence of LH stimulates ovarian theca cells to produce androgens, while FSH acts directly on ovarian granulosa cells to convert the androgens to estradiol through the action of the enzyme aromatase. FSH is additionally responsible for the recruitment of primordial ovarian follicles, as well as follicular maturation and growth, leading to the formation of a dominant follicle. During the late follicular phase, the dominant follicle produces increasing amounts of estradiol, which stimulates proliferation of the endometrial lining. As estradiol levels rise, a negative feedback loop results in decreasing levels of LH and FSH. Estradiol levels continue to rise until they reach a critical peak of approximately 200 pg/mL, where they remain for at least 36 h; during this time, the HPO feedback loop from the ovaries to the anterior pituitary switches from a negative loop to a positive loop, resulting in the phenomenon known as the mid-cycle LH surge, triggering ovulation.[2]

During ovulation, the mature follicle breaks and releases an oocyte, subsequently transforming into a corpus luteum and initiating the luteal phase. During the luteal phase, which averages 14 days in duration and is more constant in length compared to the follicular phase, the corpus luteum secretes progesterone (and smaller amounts of estradiol) under the influence of LH. Increased levels of progesterone result in differentiation of the endometrial lining from a proliferative to a secretory lining in preparation for possible implantation. Progesterone additionally increases body temperature and thickens the cervical mucus, which had remained thin and watery during the proliferative and ovulatory phases to allow for fertilization. In the absence of fertilization, the corpus luteum degenerates into the corpus albicans, resulting in decreasing circulating levels of estradiol and progesterone. The hormonal withdrawal leads to the shedding of the endometrial lining and menstruation, and the cycle begins anew.

The establishment of regular, ovulatory menstrual cycles requires maturation of the HPO axis, which does not occur concurrently with menarche, but rather in the months and years that follow. Anovulatory cycles are common in the first one to two years following menarche, with the commencement of regular ovulatory cycles occurring one to six years after menarche.[3] The onset of ovulatory cycles in adolescent girls is variable, occurring in approximately 18 to 45% of females within 2 years after menarche, in 45 to 70% of females by two to four years after menarche, and in 80% of females by 5 years after menarche.[4]

The onset of ovulatory cycles in adolescent girls is variable, occurring in approximately 18 to 45% of females within 2 years after menarche, in 45 to 70% of females by two to four years after menarche, and in 80% of females by 5 years after menarche.

Obtaining the menstrual history

The American Academy of Pediatrics (AAP) and the American College of Obstetricians and Gynecologists (ACOG) recommend discussing menstruation with all patients and inquiring about menstrual patterns regularly as a vital sign, highlighting the importance of menses as a marker of a woman's overall health.[5,6] Obtaining an adolescent's menstrual history is valuable for a myriad of reasons. First, it presents an opportunity to provide education, reassurance, and anticipatory guidance to patients and their families, normalizing the conversation about menstruation and empowering patients to understand their bodies and take charge of their health. Second, menses are an important indicator of an adolescent's health, and menstrual abnormalities can be a clue to the presence of other conditions such as eating disorders, thyroid disease, Cushing syndrome, PCOS, congenital adrenal hyperplasia, prolactinoma, an ovarian or adrenal tumor, primary ovarian insufficiency, or a bleeding disorder, among others.

Third, the recognition and treatment of identified menstrual disorders is vital for reducing morbidity in affected individuals. Menstrual disorders, particularly those characterized by significant dysmenorrhea (menstrual-associated pain) and/or heavy bleeding can negatively impact an individual's quality of life and psychosocial functioning, including their academic and work performance. Dysmenorrhea, the most common menstrual symptom affecting 70-93% of adolescents, has been associated with school absenteeism, sleep disturbance, anxiety, depression, premenstrual syndrome (PMS), and premenstrual dysphoric disorder (PMDD).[7,8] Similarly, heavy menstrual bleeding (HMB) in adolescent girls has been associated with school absenteeism and reduced quality of life.[9] Additionally, up to 20% of females with HMB will have an underlying bleeding disorder.[10] Finally, is imperative for clinicians caring for adolescent patients to be aware that, while the onset of menses represents a normal part of pubertal development for girls, it can cause significant distress for individuals who identify as transgender or non-binary, and providers must be prepared to refer patients for gender-affirming care when appropriate.

Obtaining the menstrual history is recommended at every annual health supervision visit, and when patients present for a menstrual-related complaint. It is additionally recommended that the date of the last menstrual period (DLMP) be documented at every visit. The components of the menstrual history are summarized in Table 1.

TABLE 1. Components of the menstrual history.

Components of the Menstrual History
Age of menarche
Date of last menstrual period
Cycle length*
Number of days of bleeding
Use of menstrual hygiene products and description of flow (eg. – light, moderate, heavy)
Pain associated with menses
Other symptoms associated with menses (eg. - dizziness, nausea, vomiting, diarrhea, low back pain, fatigue) and impact on functioning/activities of daily living

*Cycle length refers to the number of days from the first day of one menstrual period to the first day of the next menstrual period.

Normal menstrual patterns in adolescents

An understanding of normal adolescent menstrual patterns, including average age at menarche, expected cycle length and days of bleeding, and expected menstrual blood loss is key to providing education and reassurance to patients and families, and for identifying abnormalities that warrant further evaluation and treatment.

The current median age at menarche for women in the United States is 11.9 years, according to 2013-2017 data from the National Survey of Family Growth (NSFG), representing a small decrease from 12.1 years in 1995.[11] Specifically, 53% of women surveyed had reached menarche by age 12 years, and 90% achieved menarche by age 14.[11] Additionally, the survey found that Hispanic women were more likely compared to non-Hispanic white women to experience menarche at earlier ages (between 10 and 12 years). The median age at menarche in the United States has not changed significantly in recent decades, remaining relatively stable at approximately 12−12.5 years of age, comparable to the median age at menarche of adolescent females in other developed countries.[5] Importantly, nutritional status is one important factor known to impact the timing of menarche, with higher weight and higher body mass index (BMI) in the overweight or obese range being associated with earlier age of menarche, and low weight and low body fat percentage being associated with later age of menarche.[12−16] Specifically, in lower weight and leaner females, body fat percentage appears to be important for menarche to occur and for menses to remain regular.[17] It has been postulated that a minimum body fat percentage of 17% is required for menarche to occur, and a minimum body fat percentage of 22% is required for the maintenance of regular menses in older adolescents.[17]

The median age at menarche in the United States has not changed significantly in recent decades, remaining relatively stable at approximately 12−12.5 years of age, comparable to the median age at menarche of adolescent females in other developed countries.

Menarche typically occurs within two to three years after thelarche (the first sign of puberty in girls), typically at sexual maturity rating (SMR) 4. A lack of menses by age 15 (primary amenorrhea), or by age 14 with signs of hirsutism, concern for an eating disorder or an anatomic anomaly, or lack of development of

secondary sexual characteristics, warrants further evaluation. Similarly, a lack of menses within three years following thelarche should be investigated.

Although anovulatory cycles and irregular menstrual bleeding are common in the months and years following menarche, most adolescent cycles will be 21−45 days in length, even in the first gynecologic year, with cycles becoming more regular over time.[18−20] By the third year after menarche, the majority of menstrual cycles are 21 to 34 days in length, similar to mature adult cycles.[20] By the sixth gynecologic year (at approximately age 19-20 years), an individual's adult cycle length is established.[20,21] To that end, a lack of menses for three consecutive months, or 90 days, following menarche or following previously regular cycles should be considered abnormal and prompt further evaluation. Additionally, abnormally short cycles lasting less than 21 days, or bleeding in between cycles, should be evaluated. Infrequent or irregular menstrual periods and amenorrhea may be seen in patients with PCOS, eating disorders, chronic illnesses, thyroid dysfunction, prolactinomas, Turner syndrome, and primary ovarian insufficiency.

Finally, patient concerns regarding heavy menstrual bleeding should be taken seriously and evaluated. The normal length of a menstrual period is between three to seven days. Menses lasting eight days or longer, and/or menses associated with blood loss exceeding 80 mL are considered abnormal and indicative of heavy menstrual bleeding (HMB). Other clues to the presence of HMB include a history of soaking through menstrual products (pads or tampons) every one to two hours, requiring use of two menstrual products simultaneously (eg. − a tampon and a pad), passing blood clots larger than a quarter in size, and soiling clothing or bedsheets despite use of a menstrual hygiene product. Estimates of menstrual blood loss can be challenging based on patient report alone; however, use of three to six menstrual products per day is generally considered within the normal range. Notably, some patients may report changing menstrual products more frequently for the purposes of hygiene; thus it is important to inquire if products are soaked at the time they are changed. Use of a standardized tool such as the Pictorial Blood Loss Assessment Chart (PBAC) may be helpful to obtain a more objective measure of menstrual flow. The PBAC tool has been validated in adult women, with a score of 100 or greater indicating the presence of heavy menstrual bleeding requiring further workup and an evaluation for bleeding disorders.[10] In adolescents, heavy menstrual bleeding is most commonly due to anovulatory cycles; however, heavy bleeding from menarche, associated frequent epistaxis or gum bleeding, bleeding after dental procedures, or easy bruising should raise suspicion for a bleeding disorder such as von Willebrand disease.[22]

Conclusion

A working knowledge of normal menstrual physiology and the normal menstrual cycle in adolescents is essential to counseling patients and families, providing anticipatory guidance, and identifying abnormalities when they occur. An understanding of the normally functioning HPO axis is additionally beneficial in appreciating the pathophysiology of the myriad of menstrual disorders that affect adolescents. The chapters that follow will focus on disorders of menstruation and other menstrual concerns in adolescents, including amenorrhea, abnormal uterine bleeding, endometriosis, premenstrual syndrome and premenstrual dysphoric disorder, menstrual issues in adolescents with disabilities, menstrual suppression in transgender males, relative energy deficiency in sport (RED-S), and the effects of eating disorders and obesity on the menstrual cycle.

Declaration of Competing Interest

The author do not have any conflicts to declare.

References

1. Kives SL, Hubner N. Normal menstrual physiology. In: Neinstein LS, ed. *Adolescent and Young Adult Health Care, A Practical Guide*, 6th ed., New York, NY: Wolters Kluwer, 2016. pp. 403–4.
2. Adams JM, Taylor AE, Schoenfeld DA, Crowley WF, Hall JE. The midcycle gonadotropin surge in normal women occurs in the face of an unchanging gonadotropin-releasing hormone pulse frequency. *J Clin Endocrinol Metab* 1994;79 (3):858–64. https://doi.org/10.1210/jcem.79.3.7521353.
3. Carlson LJ, Shaw ND. Development of ovulatory menstrual cycles in adolescent girls. *J Pediatr Adolesc Gynecol* 2019;32(3):249–53. https://doi.org/10.1016/j.jpag.2019.02.119.
4. Hertweck SP. Dysfunctional uterine bleeding. *Obstet Gynecol Clin N Am* 1992;19(1):129–49.
5. American Academy of Pediatrics Committee on Adolescence, American College of Obstetricians and Gynecologists

Committee on Adolescent Health Care, Diaz A, Laufer MR, Breech LL. Menstruation in girls and adolescents: using the menstrual cycle as a vital sign. *Pediatrics* 2006;118(5):2245–50. https://doi.org/10.1542/peds.2006-2481.
6. ACOG Committee Opinion No. 651. Menstruation in girls and adolescents: using the menstrual cycle as a vital sign. *Obstet Gynecol* 2015;126(6):e143–6. https://doi.org/10.1097/AOG.0000000000001215.
7. ACOG Committee Opinion No. 760. Dysmenorrhea and endometriosis in the adolescent. *Obstet Gynecol* 2018;132(6):e249–58. https://doi.org/10.1097/AOG.0000000000002978.
8. Sachedina A, Todd N. Dysmenorrhea, endometriosis and chronic pelvic pain in adolescents. *J Clin Res Pediatr Endocrinol* 2020;12(Suppl 1):7–17. https://doi.org/10.4274/jcrpe.galenos.2019.2019.S0217.
9. Pawar A, Krishnan R, Davis K, Bosma K, Kulkarni R. Perceptions about quality of life in a school-based population of adolescents with menorrhagia: implications for adolescents with bleeding disorders. *Haemophilia* 2008;14(3):579–83. https://doi.org/10.1111/j.1365-2516.2008.01652.x.
10. Haamid F, Sass AE, Dietrich JE. Heavy menstrual bleeding in adolescents. *J Pediatr Adolesc Gynecol* 2017;30(3):335–40. https://doi.org/10.1016/j.jpag.2017.01.002.
11. Martinez GM. Trends and patterns in menarche in the United States: 1995 through 2013-2017. *Natl Health Stat Rep* 2020;146:1–12.
12. Barros BS, Kuschnir M, Bloch KV, Silva T. ERICA: age at menarche and its association with nutritional status. *J Pediatr (Rio J)* 2019;95(1):106–11. https://doi.org/10.1016/j.jped.2017.12.004.
13. Bralić I, Tahirović H, Matanić D, et al. Association of early menarche age and overweight/obesity. *J Pediatr Endocrinol Metab* 2012;25(1-2):57–62. https://doi.org/10.1515/jpem-2011-0277.
14. Currie C, Ahluwalia N, Godeau E, Nic Gabhainn S, Due P, Currie DB. Is obesity at individual and national level associated with lower age at menarche? Evidence from 34 countries in the health behaviour in school-aged children study. *J Adolesc Health* 2012;50(6):621–6. https://doi.org/10.1016/j.jadohealth.2011.10.254.
15. Huhmann K. Menses requires energy: a review of how disordered eating, excessive exercise, and high stress lead to menstrual irregularities. *Clin Ther* 2020;42(3):401–7. https://doi.org/10.1016/j.clinthera.2020.01.016.
16. Baker ER. Body weight and the initiation of puberty. *Clin Obstet Gynecol* 1985;28(3):573–9. https://doi.org/10.1097/00003081-198528030-00013.
17. Frisch RE. Fatness, menarche, and female fertility. *Perspect Biol Med* 1985;28(4):611–33. https://doi.org/10.1353/pbm.1985.0010.
18. Treloar AE, Boynton RE, Behn BG, Brown BW. Variation of the human menstrual cycle through reproductive life. *Int J Fertil* 1967;12(1 Pt 2):77–126.
19. Vollman RF. The menstrual cycle. *Major Probl Obstet Gynecol* 1977;7:1–193.
20. World Health Organization Task Force on Adolescent Reproductive Health. World Health Organization multicenter study on menstrual and ovulatory patterns in adolescent girls. II. Longitudinal study of menstrual patterns in the early postmenarcheal period, duration of bleeding episodes and menstrual cycles. *J Adolesc Health Care* 1986;7(4):236–44.
21. Widholm O, Kantero RL. A statistical analysis of the menstrual patterns of 8,000 Finnish girls and their mothers. *Acta Obstet Gynecol Scand Suppl* 1971;14(Suppl 14):1–36.
22. Yaşa C, Güngör Uğurlucan F. Approach to abnormal uterine bleeding in adolescents. *J Clin Res Pediatr Endocrinol* 2020;12(Suppl 1):1–6. https://doi.org/10.4274/jcrpe.galenos.2019.2019.S0200.