Menstruation Disorders in Adolescents

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Updated: Mar 09, 2015

Background

In adolescents, disorders of menstruation may present as abnormal uterine bleeding (AUB). Broadly understood, this term includes absence of bleeding, irregular bleeding, abnormally heavy bleeding, and bleeding in between periods.

Amenorrhea, or absent menstruation, can be either primary or secondary. Primary amenorrhea is defined as either (a) the lack of menstruation by the age of 16 years with otherwise normal pubertal development or (b) the lack of secondary sexual characteristics by the age of 13 years. Secondary amenorrhea is defined as the lack of menses for 6 months, though it is uncommon even in adolescents to lack menses for more than 3 months.[1]

AUB, as described by the International Federation of Gynecology and Obstetrics (FIGO), can be classified according to the PALM-COEIN system, in which the acronym PALM represents structural causes (*p* olyps, *a* denomyosis, *l* eiomyomas, *m* alignancy and hyperplasia) and the acronym COEIN represents nonstructural causes (*c* oagulopathy, *o* vulatory dysfunction, *e* ndometrial, *i* atrogenic, and *n* ot yet classified).[2] Once a woman has begun menarche, there are multiple menstrual disorders that can occur.

These presentations may also be associated with painful menses, known as dysmenorrhea.

Menstrual disorders in adolescents do mirror some common menstrual disorders in adults, but amenorrhea, systemic bleeding disorders, abnormal bleeding due to exogenous hormones, and sexually transmitted infections (STIs) are more common in this population. Using a systematic approach to evaluating this population will help the general practitioner diagnose and treat most of the common causative conditions. Consultation with a specialist may be necessary for complex cases or unusual disorders that are not regularly treated in a general practice.

For patient education resources, see the Women's Health Center and Pregnancy Center, as well as Amenorrhea, Vaginal Bleeding, Female Sexual Problems, Birth Control Overview, and Birth Control Methods.

Pathophysiology

In order to determine what constitutes a disorder of menstruation, it is necessary first to have a clear understanding of normal menstruation.

Puberty involves the maturation of the neuroendocrine system and requires multiple steps to achieve completion. The hypothalamus begins to secrete gonadotropin-releasing hormone (GnRH), and as secretion continues, the pituitary gonadotropins (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]) and ovarian follicles become more sensitive to stimulation.

Increases in GnRH pulsatility lead to gonadotropin secretion, eventually leading to selection of a dominant follicle. As the follicle grows, it produces estrogen, which in turn provides positive feedback on the gonadotropins to cause an LH surge and thus ovulation. In regard to the endometrium, during ovulatory menstrual cycles, the dominant follicle secretes estradiol, which causes the endometrium to proliferate, and prepare for potential implantation.

After ovulation, a corpus luteum develops as the granulosa cells become luteinized. The corpus luteum secretes progesterone, which transitions the endometrium into a more stable environment for possible implantation. Without implantation of an embryo, the corpus luteum involutes; this involution leads to falling progesterone and estradiol levels and thus to shedding of the endometrium as it loses its blood supply.

If any of the above steps is disrupted, menarche and the menstrual cycle may not occur or may occur irregularly and result in absent or abnormal menses.

In the United States, the median age of menarche is 12.43 years, with only 10% of females menstruating at 11 years and 90% by 13.75 years.[3] Non-Hispanic blacks demonstrate an earlier median age of menarche, 12.06 years, compared with 12.55 years for non-Hispanic whites.

Menarche usually occurs when females have Tanner stage IV breast and pubic hair development[4] ; the average interval from the development of breast buds to the onset of menarche is 2-3 years. In the first years after menarche, anovulatory cycles are more common and may constitute 50% of cycles. Nevertheless, most cycles are still between 21 and 45 days and last between 2 and 7 days (mean, 5 days).[5, 6]

The age of menarche is associated with the length of time needed to achieve regular ovulatory cycles. A younger age of menarche is associated with more than 50% ovulatory cycles after 1 year, whereas a later onset of menarche is not associated with fully ovulatory cycles for 8-12 years.[7]

Finally, in a normal menstrual cycle, a female will lose about 30-40 mL of blood or use approximately 3-6 pads or tampons, daily.[1] Loss of more than 80 mL of blood or bleeding that persists for longer than 7 days is an indication of abnormal menstrual flow.[8]

Etiology

Primary amenorrhea

The most common causes of primary amenorrhea are ovarian insufficiency, müllerian agenesis, and hypogonadotopic hypogonadism.[9] Pregnancy must also be considered, in that ovulation and intercourse can occur before the onset of menarche.

There are multiple ways of categorizing the causes of primary amenorrhea. One method is to group the causes according to the levels of gonadotropins and ovarian production of hormones, as follows[10] :

- Hypogonadotropic hypogonadism - Anorexia; stress- and exercise induced hypogonadism; GnRH deficiency; hyperprolactinemia; hypopituitarism
- Eugonadotropic eugonadism - Pregnancy; imperforate hymen; Asherman syndrome; müllerian agenesis; polycystic ovary syndrome (PCOS)
- Hypergonadotropic hypogonadism - Ovarian dysgenesis; ovarian insufficiency; complete androgen insensitivity syndrome; congenital adrenal hyperplasia

Another common way of organizing the multiple causes of primary amenorrhea is to categorize them on the basis of the absence or presence of breasts and a uterus, as follows:

- Breasts present, uterus present - Hypothalamic dysfunction; pituitary lesion; PCOS; ovarian insufficiency
- Breasts present, uterus absent - Müllerian agenesis; complete androgen insensitivity
- Breasts absent, uterus present - Hypogonadotropic hypogonadism; gonadal dysgenesis/agenesis
- Breasts absent, uterus absent - Enzyme deficiency (ie, 17,20-desmolase deficiency); agonadism

This categorization generally excludes etiologies associated with ambiguous genitalia, hyperandrogenism, and Cushing syndrome.[11]

Yet another method of categorizing the etiologies of primary amenorrhea involves evaluating the components of the hypothalamic-pituitary-ovarian (HPO) axis as well as the uterus and other endocrine disorders that could affect menstruation, as follows:

- I. Anatomic defects - Müllerian agenesis (Mayer-Rokitansky-Kuster-Hauser syndrome); complete androgen insensitivity syndrome; imperforate hymen; transverse vaginal septum
- II. Primary hypogonadism - Gonadal dysgenesis: Turner syndrome (45,X), Swyer syndrome (46,XY); gonadal agenesis
- III. Hypothalamic causes - Dysfunctional (stress, exercise, diet, eating disorders); Kallmann syndrome
- IV. Pituitary causes - Tumors (prolactinoma, other hormone-secreting tumors)
- V. Other endocrine gland disorders - Adrenal (adult onset adrenal hyperplasia, Cushing syndrome); thyroid disease; ovarian tumors
- VI. Multifactorial/other causes - PCOS; constitutional delay

Regardless of the manner in which one wishes to organize the causes of primary amenorrhea, evaluation of such a patient should always include certain key elements (see Presentation and Workup).

Abnormal uterine bleeding

Structural pathology is a rarer cause of abnormal bleeding in adolescents than in adults, accounting for less than 10% of abnormal bleeding in the adolescent population.[10] The most common causes of abnormal uterine bleeding in adolescents include ovulatory dysfunction, commonly due to immaturity of the HPO axis and PCOS, coagulopathy, pregnancy, and pelvic infections.[10, 12, 6]

Ovulatory dysfunction

Ovulatory dysfunction is the most common cause of AUB in adolescents. As noted

(see Pathophysiology), cycles are not consistently ovulatory for the first few years after menarche, especially if menarche occurs at a later age. During this time, the most common cause of irregular menstrual cycles is immaturity of the HPO axis, but additional etiologies should be considered, including pregnancy, PCOS, hypothyroidism, hyperprolactinemia, and functional hypothalamic dysfunction.

During anovulatory cycles, an oocyte is not released, and without the formation of a corpus luteum, progesterone is not produced. This results in endometrial proliferation from unopposed estrogen with fragile blood vessels. The endometrium irregularly outgrows its blood supply, thus leading to unpredictable, erratic,[13] and sometimes heavy and prolonged bleeding.[14]

Polycystic ovary syndrome

PCOS is the most common endocrine disorder, with a prevalence of 6-10%.[15] It is also the most common cause of irregular menstrual bleeding, oligomenorrhea, or amenorrhea, associated with hyperandrogenism.[16]

Oligomenorrhea is defined as menstrual cycles occurring more than 35 days to 3 months apart. In adolescents, oligomenorrhea may be extended to cycles that last longer than 45 days until 2-3 years after menarche, though cycles extending past 35 days may be an early indicator of irregular menstrual cycles.[17] Patients with PCOS often have few, irregular, and at times heavy cycles throughout the year.

There are multiple diagnostic criteria for PCOS, including those of the National Institute of Health, the Rotterdam Consensus Criteria, and those of the Androgen Excess Society. They all include two of three different criteria in some combination, as follows[18] :

- Hyperandrogenism (either clinical or laboratory)
- Oligoamenorrhea or amenorrhea
- Polycystic ovaries on pelvic ultrasonography

The diagnosis may be more challenging to make in adolescents, in that anovulatory cycles and acne are more common among this age group. Consequently, some have recommended that all of the Rotterdam criteria—including laboratory evidence of hyperandrogenism or progressive hirsutism, and not only acne—must be present for a diagnosis of PCOS in adolescents.[17]

Obesity is commonly associated with PCOS, because insulin resistance plays a role in the central pathophysiology of the disease,[16] but as many as 20% of adults with PCOS are not obese.[18] Metabolic syndrome is also common in PCOS adolescents,[19] which places these individuals at increased risk for cardiovascular disease and diabetes.

Additional causes should be considered in an adolescent with hirsutism and irregular menstrual bleeding, including congenital adrenal hyperplasia and ovarian and adrenal tumors. These can be ruled out by means of blood tests (see Workup).

Finally, endometrial malignancy, though rare in women younger than 40 years, should also be on the differential diagnosis for adolescents with irregular menses. Farhi et al presented a case series of 10 young women, the youngest of which was 15 years of age, all diagnosed with endometrial adenocarcinoma.[20] The most common presentation was irregular menses.

Heavy menstrual bleeding

AUB–heavy menstrual bleeding (HMB), formerly referred to as menorrhagia, is defined as blood loss exceeding 80 mL or bleeding that lasts longer than 7 days each menstrual cycle. Because objective evaluation of blood loss via the alkaline hematin method is cumbersome, AUB-HMB is often defined subjectively as excessive menstrual bleeding, even though subjective assessments of blood loss have been demonstrated to be largely inaccurate.[8]

Pictorial blood assessment charts have demonstrated high sensitivity and specificity for identifying HMB.[21] AUB-HMB can be due to uterine structural causes (eg, fibroids or adenomyosis), systemic or iatrogenic causes, and (especially important in adolescents) systemic bleeding disorders. As many as 19% of adolescents who are admitted with AUB have an underlying bleeding disorder,[22, 23] and when menorrhagia occurred from the onset of menarche, 65% of women had a bleeding disorder.[22]

Von Willebrand disease, factor deficiencies, and platelet abnormalities are the most common causes of bleeding disorders in the adolescent population, with von Willebrand disease being the most common inherited bleeding disorder.[24] Von Willebrand disease is an autosomally inherited bleeding disorder with three types and various degrees of severity. It is due to either a quantitative or a qualitative deficiency in von Willebrand factor, a protein involved in platelet adhesion.

Because menstrual bleeding is controlled by the formation of a platelet clot, HMB since menarche may be the presenting symptom in as many as 53% of patients with von Willebrand disease.[25] The prevalence is 0.8-1.3% in the general population[26] and 13-20% in those with menorrhagia.[27, 28]

The most common form of von Willebrand disease, type 1, is autosomal recessive, accounts for 70% of cases, and presents with a milder bleeding tendency as compared with the other types.[24] In addition to HMB, symptoms include epistaxis,

bleeding after dental procedures, postoperative bleeding, and joint bleeding.[29]

The American College of Obstetricians and Gynecologists (ACOG) recommends initial screening in patients with HMB since menarche,[12] as well as a history of excessive bleeding (including frequent gum bleeding) and more than two episodes of epistaxis per month or frequent bruising.[30]

Another screening tool, specifically for adolescents, includes a history of menses longer than 7 days, a "flooding" or "gushing" sensation, bleeding through a pad or tampon in 2 hours, a history of anemia, a family history of a bleeding disorder, or a history of a bleeding disorder after a hemostatic challenge, such as a tooth extraction or delivery.[31]

Intermenstrual bleeding

As the name indicates, AUB–intermenstrual bleeding (IMB), previously referred to as metrorrhagia, is defined as bleeding in between periods. Common causes in adolescents include the following:

- Pregnancy
- STIs
- Iatrogenic etiologies from administration of exogenous steroids, including oral contraceptive pills

Pregnancy, including ectopic pregnancy, can present with irregular uterine bleeding or amenorrhea.

STIs—specifically, those caused by *Chlamydia trachomatis, Trichomonas vaginalis,* herpes simplex virus (HSV), human papillomavirus (HPV), and *Neisseria gonorrhoeae* —are more common in adolescents. One survey demonstrated that among female adolescents aged 14-19 years, 24% had evidence of one of the above infections. Risk factors for STI include the following:

- Age less than 25 years
- Multiple partners
- Early age of sexual activity
- Inconsistent condom use
- Alcohol or drug consumption

Common symptoms include vaginal discharge, dysuria, and genital lesions. STIs can also cause irregular vaginal bleeding due to inflammation of the genital tract,[32] including the cervix and endometrium, which can be fragile and shed irregularly.[14]

Exogenous hormone administration, in the form of combined estrogen-progestin contraceptives, administered orally or transdermally, or progestin-only contraceptives (eg, depot medroxyprogesterone acetate, the etonogestrel implant, and the levonorgestrel-releasing intrauterine device [IUD]), can cause intermenstrual and irregular bleeding patterns.

Unscheduled bleeding is common during the first months after initiation of combined estrogen-progestin methods, and it will generally resolve after the first three cycles.[33] Unscheduled bleeding rates may be higher in those taking lower-dose pills (eg, 20 µg ethinyl estradiol) than in those taking higher-dose pills (eg, 30-35 µg).[34]

Progestin-only regimens are commonly associated with unscheduled bleeding, which may continue throughout the entire use of the medication. Although almost 50% of women will be amenorrheic after 12 months of depot medroxyprogesterone use, irregular bleeding during the first several months is common. The etonogestrel implant is associated with up to a 15% discontinuance rate due to irregular bleeding issues.[35] The levonorgestrel-releasing IUD is associated with irregular bleeding and spotting in the first 3-6 months after placement.

Finally, the nonhormonal copper IUD is associated with heavier periods and irregular bleeding during the first few months after placement, but the heavier bleeding improves over time, whereas the irregular bleeding generally does not.[36]

Dysmenorrhea

Dysmenorrhea may be either primary or secondary. Primary dysmenorrhea occurs in the absence of any identifiable pathology and is attributed to the production of prostaglandins during the menstrual cycle. Secondary dysmenorrhea occurs when there is an identifiable pelvic or hormonal pathology causing pain.

The most common gynecologic causes of secondary dysmenorrhea are endometriosis and pelvic inflammatory disease (PID). Endometriosis occurs when endometrial glands and stroma implant outside of the uterus, most commonly in the peritoneal cavity but also in the gastrointestinal tract, urinary tract, and lung. PID is a polymicrobial infection that is 10 times more common in adolescents than in adults.[10]

Clinical Presentation

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Disclosure: Nothing to disclose.

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Disclosure: Nothing to disclose.

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Disclosure: Nothing to disclose.

Acknowledgements
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Disclosure: Nothing to disclose.

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