Menstrual Disorders

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Abstract
Menstrual disorders are very common in adolescence, and can be the cause of a significant amount of stress to both the patients and their parents. Variations of the menstrual cycle in this age are very broad and are mainly caused by the immaturity of the hypothalamic-pituitary-ovarian (HPO) axis. Amenorrhea (either primary or secondary), abnormal uterine bleeding and dysmenorrhea are conditions that require careful evaluation through a stepwise and logical manner. The term primary amenorrhea refers to the condition when menarche fails to occur, while secondary amenorrhea refers to the cessation of menses once they have begun. The occurrence of irregular, prolonged or heavy abnormal uterine bleeding is one of the most urgent gynecological problems in adolescence and the diagnosis of dysfunctional uterine bleeding should be used only when all other organic and structural causes of abnormal vaginal bleeding have been ruled out. Dysmenorrhea refers to painful menstruation and is the most common reason for which a young girl may refer to a gynecologist. It is characterized as primary in the absence of an underlying organic disease, and as secondary when there is evidence of pelvic pathology. Appropriate and early management of the patient is necessary in order to minimize the possibility of future complications regarding woman’s reproductive ability.

The Menstrual Cycle in Adolescence

According to World Health Organization, adolescence is defined as the age between 10 and 19 years and is a transitional stage between childhood and adulthood, during which major physical and mental changes occur. The term ‘puberty’ refers to the sum of all the corporal and psychological changes taking place in adolescence, which lead to sexual maturation. Onset of menses is the milestone of female pubertal development and, despite international variations, usually occurs between the age of 12 and 13 years in well-nourished populations. Age of menarche showed a declining tendency from the start of the 19th century, but since the 1950s it has remained relatively
Menarche typically occurs within 2–3 years after thelarche (breast budding) at Tanner stage IV of breast development and is rare before stage III. In 98% of adolescents, menstruation will have started by the age of 15, with the median age being 12.43 years [1]. There appears to be a relationship between body weight and age at the onset of menarche, as earlier menarche has been observed in obese girls. On the other hand, malnutrition, chronic disease, eating disorders and high levels of physical activity are associated with delayed initiation of menstrual periods [2].

During the first gynecologic year (first year after menarche) the mean cycle interval is 32.2 days, varying typically from 21 to 45 days. Normal menstrual flow rarely exceeds 7 days and monthly average blood loss is estimated to 35 ml, ranging from 10 to 80 ml [3]. Early menstrual life is characterized by anovulatory cycles. The frequency of ovulation is related to both time since initiation of menses and age at menarche. Early menarche is associated with early onset of ovulatory cycles and when it occurs before the age of 12, about 50% of cycles are ovulatory in the first gynecologic year. In contrast, it may take 8 to 12 years after the first menstrual period until females with later-onset menarche become fully ovulatory. Long cycles most often occur in the first 3 gynecological years and while the age increases, menstrual cycles tend to become more regular and short. By the third year, 60–80% of menstrual cycles are 21–34 days long, as is typical in adults. An individual’s normal cycle length is established around the sixth gynecologic year, at a chronologic age of approximately 19 or 20 years. [4]

Primary and secondary amenorrhea, abnormal uterine bleeding and dysmenorrhea are conditions that can cause significant stress to both the young girl and her parents. Abnormal uterine bleeding (AUB) and especially the subtype of dysfunctional uterine bleeding (DUB) is one of the most urgent gynecological problems during this period, while dysmenorrhea is the most frequent one.

**Amenorrhea**

Primary amenorrhea is defined as the absence of menstruation in 16-year-old girls who have already developed secondary sexual characteristics, or in 14-year-old girls who have no secondary sexual characteristics development. Especially for the second group (girls with absent secondary sexual characteristics) the term ‘delayed puberty’ is more appropriate. According to the Practice Committee of the ASRM (American Society for Reproductive Medicine) and due to a trend for earlier age at menarche, adolescent females presenting with amenorrhea and normally developed secondary sexual characteristics should be evaluated by the age of 15 (2 SD above the mean age of 13). Moreover, evaluation is essential for adolescent girls presenting with amenorrhea within 5 years after thelarche – if the latter occurs before the age of 10 –, and amenorrheic girls who are above the age of 13 (2 SD above the mean age of 11) and have not yet developed secondary sexual characteristics [5].
Secondary amenorrhea is the absence of menstruation for 6 months, for adolescents who had previously irregular cycles or for those who are within the first gynecological years. Moreover for adolescents with formerly regular cycles of 21–45 days, it is defined as the absence of 3 or more subsequent menstrual periods. Overall, secondary amenorrhea is defined as the cessation of menses once they have begun.

The term oligomenorrhea (from the Greek word oligos meaning few) refers to menstrual cycles longer than 45 days. By far, most cases of oligomenorrhea occur in the first decade after menarche and the most common cause is polycystic ovarian syndrome (PCOS). Oligomenorrhea can be the menstrual disturbance prior to secondary amenorrhea and both can be evaluated following the same algorithm.

The causes of amenorrhea, without including disorders of congenital sexual ambiguity were classified in 2008 by the Practice Committee of the ASRM as follows: (a) anatomic defects of the outflow tract, (b) primary hypogonadism, (c) hypothalamic causes, (d) pituitary causes, (e) other endocrine gland disorders, and (f) multifactorial causes [5].

The problem of amenorrhea should be approached in a logical stepwise manner in order to facilitate the diagnosis. A careful medical history is the starting point of patient’s investigation, and should include information about any underlying systemic disease, family medical history and the age of menarche of the girl’s mother.

In adolescent patients with primary amenorrhea, the presence of developed secondary sexual characteristics is important and demonstrates that sexual steroids are produced and circulating. During the physical examination particular attention should be paid to signs or symptoms of systemic diseases. Per rectum gynecological examination is essential in order to assess the anatomy of the internal genitalia. Moreover, in case of reproductive tract obstruction it can reveal the presence of hematocolpos and/or hematometra (distension of the vagina and/or uterus due to blood retention within the vaginal canal or the uterine cavity, respectively).

In females with primary amenorrhea and absence of secondary sexual characteristics, measurement of FSH (follicle-stimulating hormone) and LH (luteinizing hormone) levels is recommended. Elevated gonadotrophin levels imply that the cause of the delayed puberty lies within the gonads. On the other hand, low or normal FSH and LH levels point to either constitutional delay of puberty, or hypothalamic/pituitary disorders. Further evaluation of patients with delayed puberty and elevated gonadotrophin levels, requires pelvic ultrasound imaging. This will confirm the findings of the gynecological examination and provide a clear view of the anatomy of internal genitalia (especially the presence, or not of ovarian follicles). The next diagnostic step is a karyotype study which will contribute in the differential diagnosis between ovarian failure (also referred to as ovarian insufficiency), gonadal dysgenesis, Turner syndrome and androgen insensitivity syndrome, as these are the commonest causes of primary amenorrhea in adolescent girls with the aforementioned characteristics.
Progressively deteriorating cyclic abdominal pain combined with primary amenorrhea is a strong indication of genital tract obstruction. In patients with normal pubertal development and primary amenorrhea, rectoabdominal gynecologic examination and pelvic ultrasound are essential since they can reveal the existence of congenital anatomic defects of the outflow tract. When congenital malformations of the genital tract have been ruled out for an adolescent girl with normal pubertal development and primary amenorrhea, further evaluation should be performed following the algorithm for secondary amenorrhea.

The evaluation of an adolescent patient with secondary amenorrhea should begin with pregnancy exclusion, even though a young girl may deny having had sexual intercourse. Further evaluation requires the search for signs of clinical hyperandrogenism, like acne, hirsutism, deepening of voice and clitoromegaly. Should any sign of clinical hyperandrogenism be present, FSH, LH, testosterone and DHEA-S (dehydroepiandrosterone sulfate) must be measured. When a mild to moderate elevation of testosterone levels along with an LH/FSH ratio above 2 is observed, PCOS is the most probable diagnosis. DHEA-S serum levels between 500 and 700 mg/dl require further investigation of the adrenal gland function, with serum 17OH-progesterone concentration measurement. DHEA-S serum levels above 700 mg/dl suggest that the cause of hyperandrogenism is the late onset type of congenital adrenal hyperplasia. In patients with secondary amenorrhea and normal serum androgen levels, despite the presence of clinical hyperandrogenism, progesterone challenge test should be performed in order to assess the levels of circulating estrogens and their effect on the endometrial function.

Secondary amenorrhea along with absence of clinical hyperandrogenism signs requires measurement of FSH, LH, TSH (thyroid-stimulating hormone) and prolactin levels, as amenorrhea may also be the result of hyperprolactinemia or thyroid gland disease. TSH levels that are either lower or higher than normal range indicate that thyroid disease may be the reason of amenorrhea. A significant elevation of PRL levels (>100 ng/ml) suggests the existence of a pituitary adenoma, while mildly elevated PRL is usually the result of dysregulation in secretion inhibition mechanisms (use of antipsychotic drugs, hypothyroidism, pressure effect on the pituitary stalk). Magnetic resonance imaging (MRI) of the pituitary fossa should be performed in patients with persistent, refractory, or excessive (>100 ng/ml) hyperprolactinemia, which is not related to hypothyroidism and antipsychotic drug use, as it can reveal the presence of lesions in the pituitary gland [6]. If FSH and LH levels are above normal range, measurement must be repeated. If elevation is persistent, in several consecutive measurements, along with normal TSH and prolactin levels, the most probable cause of the secondary amenorrhea is ovarian failure [7]. When FSH, LH, TSH and prolactin levels are within the normal range, progesterone challenge test must be performed. If there is no withdrawal bleeding after the test, an estrogen-progesterone challenge test must be performed to ensure the normal endometrial function.
Dysfunctional Uterine Bleeding – Abnormal Uterine Bleeding

DUB refers to endometrial bleeding that is prolonged, excessive, irregular and not attributable to any underlying structural or systemic disease. Bleeding associated with organic causes such as pregnancy complications, clotting abnormalities, systemic diseases, reproductive tract’s pathology, endocrine disorders and iatrogenic causes is defined as AUB [8]. In the USA, the definition of DUB refers to anovulatory bleeding. On the other hand, the European Society of Human Reproduction and Embryology (ESHRE) defined DUB as excessive (by means of severity, duration, or frequency) bleeding of uterine origin, which is not due to demonstrable pelvic disease, complication of pregnancy or systemic disease. Therefore, according to ESHRE, DUB can be either ovulatory or unovulatory.

Differential diagnosis of abnormal uterine bleeding during adolescence should firstly exclude pregnancy-related hemorrhage, as it can pose patient’s life at risk. Spontaneous, threatened or incomplete abortion, ectopic pregnancy, post-abortion endometritis or hydatidiform mole are possible diagnoses in this category.

Bleeding disorders should also be excluded, especially in patients presenting with AUB during their first menstrual cycles. One of the initial processes to control blood loss during menstruation is the formation of intravascular platelet plug. Thus, quantitative reduction or functional abnormality of platelets can lead to increased menstrual blood loss. Defects in the coagulation cascade can also lead in AUB [9]. Almost 19% of adolescents with persistent menorrhagia requiring hospital admission have coagulation disorder, and more than 50% of these young women have a coagulopathy such as thrombocytopenia, von Willebrand disease or leukemia [10]. Systemic bleeding disorders are found in 7–20% of women of all ages presenting with menorrhagia [11]. von Willebrand factor's deficiency is a common hereditary bleeding disorder associated with AUB. Especially, among women with von Willebrand’s disease, 65% report heavy bleeding at menarche. Factor XI deficiency, Glassman’s disease (defective platelets) and aplastic anemia are also associated with AUB. Therefore, systemic bleeding disorders must be of primary consideration in adolescents who present with menorrhagia at menarche or who require hospital admission [12].

Chronic diseases affecting renal or liver function may result in AUB especially if end stage. Such diseases are, however, rare in adolescence. Deficiency of vitamin K-dependent (II, VII, IX, X) or other clotting factors (including fibrinogen and plasminogen) are common among patients with liver disease [13]. Abnormal estrogen metabolism may also result from liver disease causing endometrial proliferation and estrogen breakthrough bleeding. Uremic patients suffer from abnormal platelet function which leads to excessive menstrual bleeding.

Abnormal uterine bleeding can also occur due to reproductive tract diseases. Trauma and genital injury due to rape, sexual abuse or consensual sexual intercourse could result in severe bleeding. Self-injury may result when attempting to insert tampons or other foreign objects in the vagina. Endometritis and pelvic inflammatory
disease (PID) due to chlamydia and gonorrhea can cause AUB during adolescence in a frequency of less than 10% of all AUBs. Vaginitis, cervical inflammation or erosion have the potential to cause vaginal bleeding that the patient may interpret as irregular menstruation. Finally, partially obstructive congenital anomalies of the genital tract, such as transverse septa or functional communicating rudimentary uterine horn, could manifest with intermenstrual bleeding.

Various clinical manifestations may coexist along with AUB, and usually signal an underlying endocrine disease. Clinical signs of hyperandrogenism like severe acne, facial and other male pattern hair growth and central obesity may suggest polycystic ovarian syndrome. The adrenal glands can also be a source of androgens and diseases like congenital adrenal hyperplasia, Cushing's disease, adrenal insufficiency and adrenal androgen-secreting tumors (when adrenal glands overproduce androgens) may be associated with signs of severe hyperandrogenism and anovulatory cycles. Hypothyroidism is another cause of menorrhagia and is accompanied by thermoregulatory or metabolic symptoms. Ovarian causes of anovulatory AUB include abnormal function of corpus luteum, steroid-secreting ovarian tumors and imminent premature ovarian failure.

Finally AUB can occur due to iatrogenic causes, e.g. administration of hormonal medications, including intramuscular or subcutaneous implants, IUDs, combined oral contraceptives, combined transdermal patches and vaginal rings. Other drugs associated with AUB, include anticoagulants, neuroleptics and chemotherapeutics.

The causes of abnormal uterine bleeding are summarized in table 1.

Clinical evaluation of the patient presenting with AUB should begin with a careful medical history of the patient, as it can reveal any potential underlying condition. Primary target in the diagnostic algorithm of AUB is to locate the source of bleeding and secondary to rule out all the above-mentioned organic causes. It is important to obtain information about patient's menstrual history, and particularly about age at menarche and length of cycles. The patient should also be asked about the duration of bleeding, the quantity and the amount of blood, the presence (or absence) of clots and the possible presence of pain or cramping. The review of systems should specifically address other unusual or abnormal bleeding, psychosocial stressors, recent weight changes, eating and exercise habits, substance use, and signs of hyperandrogenism (acne, hirsutism). The family history should be reviewed for endocrinopathies and hematologic disorders such as thyroid disorders, functional ovarian hyperandrogenism and von Willebrand's disease. The patient should be asked, in private, about sexual activity, use of contraception, and history of sexually transmitted infections. Diagnosis of DUB is established, only when all of the aforementioned organic causes have been ruled out.

AUB and especially the subtype of DUB is one of the most urgent gynecological problems during adolescence. Treatment of patients with DUB should firstly focus to control bleeding and regulating menstruation. Anemia correction and iron stores replenishment is the second goal of the therapeutic strategy. In the majority of the
cases, hormonal treatment is indicated, but the specific kind and way of hormonal therapy will be dictated by the severity of DUB [3].

In patients with mild DUB, menses are slightly prolonged or irregular, with hemoglobulin levels above 12 g/dl. Hormonal therapy is rarely indicated and patient reassurance and education about the normal menstrual cycle are usually sufficient. Careful follow-up along with appropriate education regarding menstrual calendar keeping will make the adolescent feeling safe [14].

Moderate DUB is characterized by prolonged, profuse menses, impeding daily activities, or by a clearly shortened menses interval accompanied by mild anemia (hemoglobulin levels above or equal to 10 g/dl). Treatment of choice includes the administration of low-dose oral contraceptives or cyclic progestogen. Cyclic oral progestogen is administered for the same 10 days of every month in order to stabilize the endometrium, preventing the action of unopposed estrogens. Consistent

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iron deficiency anemia can be treated with supplemental oral iron therapy. Nonsteroidal anti-inflammatory drugs (NSAIDs) can also reduce the flow by nearly 50%, in patients with uterine bleeding, through inhibition of prostaglandins’ synthetase. Treatment with oral contraceptives should be continued for at least 3–6 months [3].

Heavy bleeding and hemoglobin levels less than 10 g/dl suggest severe DUB and patients usually require hospitalization. In hypovolemic patients, immediate resuscitation with intravenous fluids for volume expansion and possible transfusion are indicated in order to restore hemodynamic balance. Blood samples must be obtained to exclude an underlying bleeding disorder before starting therapy. Intravenous conjugated equine estrogens have been used during the previous years, being highly effective in controlling uterine bleeding, but they are not available any more. Nowadays, intramuscular medroxyprogesterone acetate together with combined oral contraceptives (COCs) can be administered, as they provide faster results in controlling heavy menstrual bleeding. Hemorrhage usually stops within 24 h and continuation of therapy with COCs alone is in most cases recommended. Dilation and curettage, although not usually performed in adolescence, is indicated in the rare cases in which hormonal treatment is unsuccessful.

After hemodynamic stabilization, the adolescent girl can be treated with COCs [3]. A tablet of COCs containing a high dose of estrogen should be taken every 6 h, along with an antiemetic if nausea is present. After a maximum of eight doses during 48 h, the dose must be tapered over 3 days to one pill daily. Patient will then begin a new COCs pack with the same amount of estrogen for the next 21 days taking one pill daily.

Tranexamic acid is a synthetic derivative of the amino acid lysine, which exerts an antifibrinolytic effect through reversible blockade on plasminogen. The drug has no effect on blood coagulation parameters or dysmenorrhea, with one third of women experiencing side effects, including nausea and leg cramps. Administration of 1 g of tranexamic acid every 6 h for the first 4 days of the cycle can reduces menstrual blood loss by up to 40%, as has been demonstrated by 10 randomized placebo-controlled trials. Other therapies, such as high doses of progestogens given per os or intramuscularly, Gn-RH agonists with add-back therapy and levonorgestrel impregnated IUDs have little place in adolescent’s DUB management [15].

**Dysmenorrhea**

Dysmenorrhea is the most common problem in adolescence and presents as painful menstruation. The word ‘dysmenorrhea’ is originated from the Greek language and denotes a difficulty in menses’ outflow.

Dysmenorrhea is characterized as primary in the absence of an underlying organic disease, and as secondary when there is evidence of pelvic pathology.
Primary Dysmenorrhea

Primary dysmenorrhea has a high prevalence in adolescence [16], and is usually observed after the first gynecological years along with the onset of ovulatory menstrual cycles.

COCs and NSAIDs are the most frequently used agents in the treatment of primary dysmenorrhea. Combined oral contraceptives have a beneficial effect on dysmenorrhea by inhibiting ovulation, leading to suppression of endometrial tissue growth and, secondary, to reduction of menstrual flow below normal levels. It also seems to result in a concomitant drop of menstrual prostaglandins’ levels. Therefore, the lessening of menstrual flow along with the decrease of prostaglandins’ reduces uterine motility and ischemia and thus uterine cramping pain [17]. NSAIDs are the most commonly used medical treatment for dysmenorrhea. More research is needed in order to explore whether specific COX-2 inhibitors are effective in treating dysmenorrhea in the adolescent age group.

In case of no response to neither of the aforementioned treatment methods, laparoscopy and/or hysteroscopy are indicated [18].

Secondary Dysmenorrhea

By definition secondary dysmenorrhea implies organic pelvic lesion. As mentioned above any menstrual pain arising more than 3 years after menarche must be considered to be of pathologic origin. Chronic pelvic or low abdominal pain, beginning one or two days prior menses, irregular or heavy menstrual patterns, dyspareunia and bowel symptoms are signs usually associated with an underlying organic pathology. Patients with secondary dysmenorrhea usually outline several different clinical symptoms in their menstrual history rather than the predictable ones typically described by patients suffering from primary dysmenorrhea.

Endometriosis and pelvic inflammatory disease are the most frequent causes of secondary dysmenorrhea in adolescence. Malformations of the Mullerian ducts in this age group must be considered as a distinct option. Other infrequent causes of secondary dysmenorrhea during adolescence are uterine retroversion in fixed position, stenosis of cervical channel, intrauterine devices without progestin-containing system, uterine fibroids, endometrial or endocervical polyps, adenomyosis and pelvic venous congestion [18].

Dysmenorrhea associated with chronic pelvic pain due to endometriosis is less likely to respond to NSAIDs or combined oral contraceptives. If this lack of response to NSAIDs and COCs happens after at least 3 months of therapy, laparoscopy is indicated. Pelvic examination may elicit mild to moderate tenderness. Uterosacral nodules and pelvic masses are rare findings in patients with endometriosis of this age group. Laparoscopy is the single most useful diagnostic procedure because most adolescents
have minimal or mild stages of endometriosis. Cervical and vaginal cultures, pelvic ultrasonography, magnetic resonance imaging, hysterosalpingography and hysteroscopy can also be helpful in the evaluation of secondary dysmenorrhea. It should be noted that management of secondary dysmenorrhea must target towards the treatment of the underlying organic pathology along with the treatment of pain.

The algorithm of evaluation and management of both primary and secondary dysmenorrhea is demonstrated in figure 1.

**Fig. 1.** Evaluation and management of dysmenorrhea.

### References


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