Menstrual Disorders in Adolescent Females: Current Concepts

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Introduction

The onset of menstruation (ie, *menarche*) is a seminal event of the adolescent female signifying the progress of puberty, which in the majority of cases is visibly initiated with *thelarche* (onset of breast development or breast buds). Menarche usually occurs during the earlier time of the second decade of life and ends with menopause, typically in the fifth decade of life.[1] The adolescent can present with a wide variety of menstrual dilemmas and disorders. After an introduction that includes a synopsis of menstrual physiology, many of these menstrual conditions are considered in this discussion, including dysfunctional uterine bleeding (DUB), amenorrhea (primary and secondary), and dysmenorrhea (primary and secondary).[1,2]

Physiology of Menstruation

Puberty is the period involving the development of secondary sexual characteristics and the attainment of sexual reproduction capacity.[3] The transition of puberty occurs usually between 10 and 16+ years of age and is impacted by several hormones, which affect the cellular and glandular components of the reproductive system, leading to the anatomical changes of puberty. Thelarche occurs on average between 10 to 10.5 years of age with a range of 8 to 13 years in Caucasian females and earlier in African-American females.[4,5] Menarche occurs on average at 12.0 years of age in African-American females and 12.6 for Caucasian females; a wide range is noted from 9 to 16 years.[4,5] The development of regular ovulatory menstrual cycles may take 1 to 5 years after menarche as the hypothalamic-pituitary-ovarian axis continues to mature.[1,6] Table 1 provides definitions for important menstrual disorders.

Dis Mon 2009;55:45-113
0011-5029/2009 $36.00 + 0
doi:10.1016/j.disamonth.2008.10.004

TABLE 1. Menstrual disorders definitions*

1. Normal adult menstrual cycle
   a. Mean interval of 28 days (±7 days)
   b. Duration of menses of 4 days (±2-3 days)
   c. Median blood loss is about 30 mL per month (with the upper limit of normal defined as 60-80 mL per month)
2. Amenorrhea: absence of menses; can be primary or secondary (absence of three consequent menstrual cycles, after regular periods have been established)
3. Oligomenorrhea: infrequent, irregular bleeding at >45-day intervals
4. Menorrhagia: prolonged (>7 days) or excessive (>80 mL) uterine bleeding occurring at regular intervals
5. Metrorrhagia: uterine bleeding occurring at irregular but frequent intervals, the amount being variable
6. Menometrorrhagia: prolonged uterine bleeding occurring at irregular intervals
7. Hypermenorrhea: synonymous with menorrhagia
8. Polymenorrhea: uterine bleeding occurring at regular intervals of <21 days
9. Dysfunctional uterine bleeding: abnormal (different from that patient's normal) uterine bleeding that is unrelated to any anatomic lesion

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TABLE 2. Hormones secreted by the hypothalamus

Gonadotropin releasing hormone (GnRH)
Thyrotropin releasing hormone (TRH)
Growth hormone releasing hormone (GHRH)
Corticotropin releasing hormone (CRH)
Somatostatin
Dopamine

Physical changes in breast and pubic hair development as well as in somatic growth present clear evidence of the pubertal process. Various hormonal changes precede these physical changes by years and involve the hypothalamic-pituitary-gonadal axis that has a feedback loop with both inhibitory (negative) and stimulant (positive) processes. Several hormones are secreted by the hypothalamus, as noted in Table 2. Many of these hormones are short-acting and are released during late childhood at night, with increasing pulsatile frequency into the portal circulation of the hypothalamus.

GnRH pulsatile secretion from the arcuate nuclei in the hypothalamus eventually leads the anterior pituitary to release the gonadotropins, follicular-stimulating hormone (FSH) and luteinizing hormone (LH), leading to stimulation of the sex (gonadal) steroids, estrogen, and progesterone. FSH stimulates estrogen production and LH stimulates

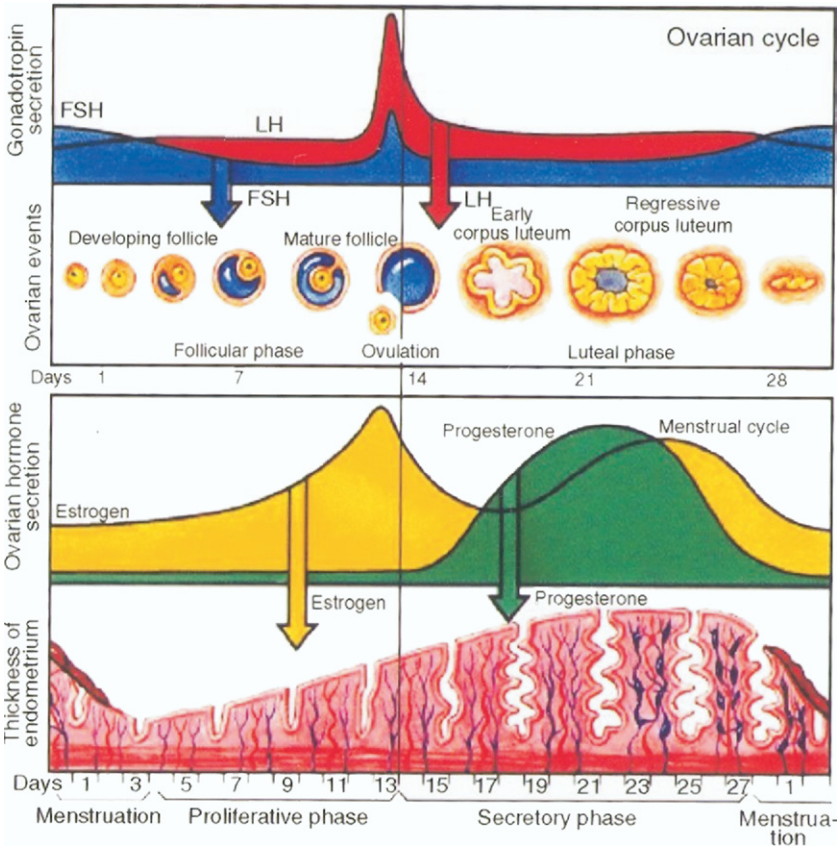

FIG 1. Normal menstrual cycle. (Reprinted with permission from: Greydanus DE, Feinberg AN, Patel DR, Homnick DN, eds. The Pediatric Diagnostic Examination. New York, NY: McGraw-Hill Medical Publishers, 2008.) (Color version of figure is available online.)

androgen production, with resultant development of breasts, pubic hair, and testicular enlargement in males. A negative or inhibitory influence on the hypothalamus is induced by estrogen and progesterone. The menstrual cycle is generally divided into three phases (Fig 1): *follicular phase* (the first phase), *ovulation* (the second phase), and the *luteal phase* (third or final phase). The *fertile window* is noted between the first and third phases. The hypothalamus serves as a generator of puberty, while GnRH serves as a regulator controlling menstrual cycling.

Follicular Phase

This initial phase of the menstrual cycle involves ovarian follicle development and endometrial growth stimulation over an approximate

14-day time period. The main hormone in this phase is estrogen and its production depends on various hormones, including GnRH, FSH, LH, and inhibin. GnRH moves through the portal plexus of the hypothalamus to the anterior pituitary gland to stimulate the production of FSH and LH. The production rate of these pituitary gonadotropins depends on the secretion of estrogen and progesterone from the ovaries, as well as GnRH from the hypothalamus. Hypothalamic, pituitary, or ovarian dysfunction can all lead to menstrual disorders.[7,8]

Ovulation

Ovarian follicles remain in cycles of growth and atrophy during the menstrual life of the female. The rise of FSH a few days prior to menstruation stimulates FSH receptors in ovarian follicles with resultant development of various follicles (typically 3 to 11), and the follicle with the highest FSH sensitivity is destined to be the dominant follicle of that specific cycle.[9,10] Estrogen is released from the developing follicle, while the glycoprotein, FSH, affects the follicular granulosa cells for ongoing growth as well as increase in LH receptors. The glycoprotein, LH, affects the theca cells of the maturing ovarian follicles with resultant androgen production. Androgen to estrogen conversion is enhanced by FSH because of increased follicular aromatase activity and further follicle maturation.

There is a negative feedback loop in which estrogen from the dominant ovarian follicle reduces pituitary FSH production while a positive feedback loop allows increased LH secretion. Inhibins A and B are hormones that are secreted by the ovarian follicle with resultant pituitary feedback to reduce FSH production, while activins raise follicular sensitivity to LH.[11] The result is continued maturation of the dominant follicle over that of the other maturing follicles. Levels of estrogen rise until approximately the first 14 days (day 13 or 14) of the menstrual cycle, when a critical estrogen level is reached that induces a major increase in LH (LH peak or surge) and resultant ovulation.

The ovulatory part of the menstrual cycle usually occurs over a 1- to 2-day time period and initiates the final menstrual phase, the luteal phase. The LH surge that occurs in the middle of the normal menstrual cycle leads to ovulation and the release of the oocyte from the dominant ovarian follicle and also the resumption of meiosis of the oocyte. Gradual progesterone increase is noted during the 24 hours prior to and after ovulation and, if pregnancy does not occur, the follicle becomes the corpus luteum that mainly produces progesterone in a sustained fashion.

Luteal Phase

The surge of LH production occurs in the middle of the menstrual cycle, resulting in ovulation that lasts 1-2 days and creates a window of fertility of approximately 6 days; the length of the fertile window depends on various factors, including gynecological age and actual menstrual length. The dominant ovarian follicle is released and becomes the corpus luteum, producing persistent secretion of progesterone over a timeline of approximately 12 days, unless normal pregnancy occurs with resultant human chorionic gonadotropin production. Ovulation-induced progesterone secretion leads to a period of altered glandular secretion and stromalchanges, preparing the endometrium for possible implantation of a blastocyte. The increased progesterone reduces pituitary FSH and LH secretion via a negative feedback loop and also reduces GnRH pulsatile secretion that results in less gonadotropin secretion (ie, FSH and LH).[12]

The rise in estrogen in the early follicular phase leads to estrogen binding with endometrial receptors, growth factor stimulation with resultant blood vessel stabilization, and growth of endometrial tissue, including spirol arterioles, stroma, and glands. Postovulatory rise in progesterone leads to transformation of the endometrium from a proliferative to a secretory state, with glands that are more and more tortuous, with production of secretions rich with glycogen and preparing for implantation. The endometrium becomes edematous and very vascular.

If pregnancy does not occur, the natural life of the corpus luteum ends on the 14th day of the luteal phase and as it involutes, there is a dramatic reduction in progesterone that induces menstruation. As the progesterone production is reduced, pulsatile GnRH production rejuvenates and a new menstrual cycle is reborn with the potential of another pregnancy. Menstruation (menstrual period; menses) is the term that refers to the bleeding event that results when the endometrium desquamates, due to the withdrawal of estrogen and progesterone.

Initial effect of hormone withdrawal is reduction of half of the endometrial mass tissue because of fluid absorption and vasoconstriction of spiral arterioles, mainly under the influence of prostaglandin F2α (PGF2α) and endothelin-1 with resultant reduction in blood flow. The periodic vasoconstriction (over 24 hours) and relaxation of endometrial arterioles results in endometrial ischemia that helps to induce local release of cytokines (as tumor necrosis factor alfa) and other signaling molecules.[13] There is also loss of hyaluronic acid and water from the

regressing endometrium, as well as major extracellular matrix destruction noted just before and during menses.[14] Also noted is activation of proinflammatory cytokines and matrix metalloproteinases (MMP-1, MMP-3, MMP-9) in the endometrium that contribute to tissue breakdown independent of the vasoconstriction physiology.[11,15,16]

Finn has contended that the process of menstruation is an *inflammatory* one with edema of tissues, migration of leukocytes, and decidual cells, suggesting granulation tissue fibroblasts.[17] Indeed, there are various inflammatory cells present, including macrophages, granulated lymphocytes, and polymorphonuclear leukocytes that contribute to vascular permeability and breakdown of endometrial tissue via release of various regulatory molecules. Interleukin-8 is a cytokine that leads to the release of various chemicals, such as tryptase and chymase, with resultant influence on leukocyte migration to the endometrium that helps induce endometrial breakdown.

Essential to normal menstruation is normal blood coagulation with generation of thrombin-induced fibrin that is stimulated by tissue factor in the endometrium via the extrinsic pathway. Tissue factor rises in decidual cells of the endometrium because of progesterone and tissue factor falls with the fall of progesterone. It is noted that fibrin-plate plugs are found in superficial blood vessels and not in the surrounding tissue because of endometrial fibrinolytic pathways. A balance is necessary to be achieved between the coagulation factors' production that controls bleeding and the process of fibrinolysis that stops clot organization and intrauterine adhesion. Indeed, the coagulation process is mainly one of hemostasis in the secretory menstrual phase and a fibrinolytic process in overt menses. As apoptosis and necrosis continues, endometrial tissue shrinks and much of this layer breaks down into fragments with much blood and fluid that are expelled into the uterine cavity and lost.

Eventually the blood loss stops, and repair of tissue occurs because of increasing estrogen with local growth factors release and sustained vasoconstriction. Vascular endothelial growth factor (VEGF) is an angiogenic chemical that is induced by hypoxia and is vital to the overall endometrial repair process.[18] The process of endometrial angiogenesis is a complex one and related to influence of VEGF and the fibroblast growth factors that are produced, in part, by the migration of leukocytes to the endometrium.[19-21]

After ovulation, the corpus luteum leads to progesterone production that changes the endometrium to a secretory state, with a decidualized stroma that has increased edema and vascularity along with glands that are

tortuous and abundant in glycogen. As the corpus luteum dies, both estrogen and progesterone rapidly decrease, with resultant endometrial atrophy and loss of approximately 50% of the endometrial mass in 24 hours. Vascular vasoconstriction leads to the end of menstruation. Disruption in this process of angiogenesis leads to menstrual dysfunction and abnormal bleeding. Failure to develop a fully mature secretory endometrium characterizes a luteal phase defect.[22,23]

Dysfunctional Uterine Bleeding (DUB)

DUB, one of the most urgent adolescent gynecological conditions, refers to prolonged, excessive, or unpatterned uterine endometrial bleeding not caused by uterine anatomical conditions.[1,24] Causes of abnormal menstrual bleeding are noted in Table 3 and include coagulation disorders, infections, trauma, pregnancy complications, systemic conditions, local lesions, and various reproductive tract pathology; these etiologies need to be eliminated before using the diagnosis of DUB.[1,6,25] Premature menarche has been noted on occasion in girls in which one or more episodes of vaginal bleeding occurs without evidence of pubertal changes; it is usually idiopathic but may be associated with hypothyroidism or other causes.[26,27]

Approximately 15% of adult women present with DUB and this number is much higher in the adolescent female population. One questionnaire-based study of 1410 high school females with a mean age of 16.7 years revealed that 37% had a history of heavy menstruation, 38% had a family history positive for heavy menses, and 22% of these adolescent females had been treated with hormonal therapy for their menstrual condition.[28] Complications in cases of coagulation disorders include anemia, spontaneous bleeding into joints or muscles, increased bleeding after surgery, and increased absence from school and/or work.

A major cause of DUB in adolescents is anovulatory irregular menstruation, typically due to lack of the positive feedback effect of estrodiol and absence of ovulation at menarche and for 1-5 years after menarche.[29] For example, research notes that anovulation occurs in 55%-82% of menstrual cycles in adolescents at menarche and for 2 years after menarche, while anovulation occurs in 30%-45% of menses from years 2 to 4 after menarche, and no more than 20% of menses from years 4 to 5.[30]

Levels of the glycoproteins LH and FSH, as well as the hormones estrogen and progesterone, are below that of normal adult female levels during the first year after menarche. While estradiol levels increase to normal adult levels by year 2 postmenarche, progesterone

TABLE 3. Causes of abnormal menstrual bleeding in adolescents* (Exclude rectal, urethral, and other perineal bleeding)

- Vaginal or uterine abnormalities
  - Trauma (coitus, rape, abuse)
  - Foreign body (IUD, tampon, etc)
  - Infection
    - Vaginitis (trichomonas, gonorrhea)
    - Cervicitis
    - Endometritis (tuberculosis)
    - Pelvic inflammatory disease
    - Sexually transmitted condylomata (HPV) of cervix or vagina
  - Tumor
    - Botryoid sarcoma
    - Polyps (uterine, cervical)
    - Ovarian cyst or tumor (mature teratoma, endometrioma)
    - Leiomyomatosis
    - Clear cell carcinoma of cervix or vagina (DES)
    - Other ovarian malignancy and metastatic malignancy
  - Endometriosis
  - Congenital malformations of uterus
- Complications of pregnancy
  - Threatened or spontaneous abortion
  - Ectopic pregnancy
  - Molar pregnancy
  - Induced abortion
- Coagulopathy
  - Generalized
  - Thrombocytopenia (idiopathic thrombocytopenic purpura; leukemia; lymphoma; aplastic anemia, hypersplenism)
  - Platelet dysfunction (Glanzmann's disease)
  - Clotting disorders (hemophilia; von Willebrand's disease; other coagulation factor deficiencies)
  - Uterine production of menstrual anticoagulants
- Dysfunctional uterine bleeding
  - Normal variation
    - Midcycle ovulatory bleeding
    - Early postmenarcheal anovulation
    - Early postmenarcheal estrogen irregularities
  - Chronic anovulation
  - Exogenous steroids
  - Oral contraception
    - Midcycle breakthrough bleeding
    - Relative luteal progesterone deficiency
  - Progestogens (oral agents; Norplant; Depo-Provera)
  - Continuous estrogens
  - Other drugs
    - Danazol
    - Spironolactone
    - Anticoagulants
    - Platelet inhibitors
    - Chemotherapy drugs
    - Natural hormones from plant extracts (DHEA, Dong Quai, Yam Extract)

TABLE 3. Continued . . .

Systemic diseases
Hyperthyroidism or hypothyroidism
Adrenal insufficiency
Cushing's syndrome
Diabetes mellitus
Chronic liver disease
Crohn's disease; ulcerative colitis
Chronic renal disease
Systemic lupus erythematosus
Ovarian failure
Hyperprolactinemia
Androgen excess
Exogenous androgens, PCOS, congenital adrenal hyperplasias
Androgen-producing ovarian or adrenal tumor
Estrogen excess
Granulosa-theca cell tumor of the ovary
Other tumors
Hypothalamic
Emotional stress
Physical stress, especially exercise
Ovulatory
Short luteal phase
Prolonged luteal phase (Halban's disease)
Luteal progesterone insufficiency

Abbreviations: IUD, intrauterine device; HPV, human papillomavirus; DES, diethylstilbestrol.

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levels remain low for up to 5 years after menarche, and LH/FSH are at adult levels by year 5. LH secretion is mainly nocturnal and episodic before puberty and, as puberty develops, LH secretion increases and normal timing of LH pulses are necessary for developing normal ovulatory cycles.

Increased estrogen leads to less GnRH with reductions in FSH and LH and resultant less stimulation of estrogen that can lead to vasoconstriction and atrophy of thickened endometrium and resultant heavy, prolonged menstrual bleeding. Estrogen that is unopposed by progesterone leads to growth of the endometrium that eventually cannot be supported by its blood supply and results in partial endometrial breakdown with irregular shedding and bleeding. Failure of ovulation and resultant unopposed estrogen leads to decreased vascular tone of endometrial blood vessels, with inhibition of vasopressin release and resultant vasodilatation and increased menstrual bleeding.[31] Unopposed estrogen also induces VEGF production with

TABLE 4. Coagulation disorders

Hemophilia A (F [factor] VIII deficiency)
Hemophilia B (F IX deficiency)
Von Willebrand's Disease (vWD)
Platelet function defect
Thrombocytopenia
Factor deficiencies: F V, XI, XIII, VII, II
Fibrinogen deficiency
Others

resultant angiogenesis.[31] The endometrium that is not exposed to progesterone produces less prostaglandin (PG) and a greater ratio of PGE than PGF. Excessive blood loss may also be due to increased development of endometrial nitric oxide (endothelium-derived relaxing factor) that is stimulated by unopposed estrogen.[32]

Although anovulation is the main stimulant to DUB, abnormal menstrual bleeding can also occur in *ovulatory* states, as, for example, in the Halban syndrome or prolonged progesterone in which a persistent corpus luteum cyst leads to 6 to 8 weeks of amenorrhea, followed by irregular menses.[22,23]

Coagulation and DUB

An important aspect of normal blood clotting in controlling menstrual bleeding is the generation of thrombin-induced fibrin, as induced in the endometrium by tissue factors utilizing the extrinsic pathway of coagulation.[6] Fibrin-platelet plugs develop in superficial blood vessels due to endometrial fibrinolytic pathways and there is a balance between coagulation factors that control bleeding and fibrinolysis to prevent organization of clots and intrauterine adhesion. In menstruation, there is a shift to fibrinolytic mechanisms with endometrial breakdown and shedding of uterine material that is expelled with variable loss of tissue and blood.

Eventually, prolonged vasoconstriction occurs along with local growth factors that are released and increase in estrodiol production that stops blood loss. Repair of epithelium develops with the production of angiogenic factors such as VEGF that is stimulated by hypoxia.[6] Angiogenesis in the endometrium involves the formation of new vasculature from preexisting vessels because of the effects of VEGF and fibroblast growth factor. Migratory leukocytes are an important part of this cyclical angiogenesis, as noted earlier.

Congenital Coagulation Disorders

Severe dysfunctional uterine bleeding may be the first indication of an underlying bleeding disorder (Table 4). Studies note that 19%-28% of adolescents who are hospitalized due to acute menstrual bleeding have a coagulation disorder.[33,34] Approximately 80%-85% of inherited bleeding disorders are Hemophilia A (F [factor] VIII deficiency), von Willebrand's Disease (vWD), and Hemophilia B (F IX deficiency).[1,9,35,36] Approximately 15% are congenital bleeding disorders that include deficiencies of fibrinogen, prothrombin, and factors V, VII, X, XI, XIII and combined V + VIII.[1,36-38] Approximately 20%-30% of those with menorrhagia have platelet dysfunction, while 13%-17% have vWD.[25]

von Willebrand's Disease. vWD is an autosomally inherited condition affecting 1%-3% of the population and caused by a gene on chromosome 12. vWD is either a quantitative or a qualitative defect of the production of vW factor; this factor is a protein needed for normal platelet adhesion at injured endothelium and for preservation of circulatory Factor VIII.[36] Clinical findings and laboratory evaluation will identify vVD including *Quantitative* types 1 or 3 and *Qualitative* 2, with its various subtypes: 2a, 2b, 2m, and 2n.

The mildest vWD type is one with only moderate vW factor reduction and this involves 70%-80% of this disorder. Both types 1 and 2 are often not identified until adolescence or adulthood, in which suspicion arises after bleeding is noted with severe trauma or surgery. Suspicion may also develop because the adolescent female presents with menorrhagia as her first clinical evidence of vWD. The first report of vWD was by Dr. Erik von Willebrand in 1926 in which 16 of 23 affected family members were female and the index case was a young adolescent female who died at age 13 from uncontrolled bleeding during her fourth menstrual period; she probably was a type 3 vWD.[39] A number of adult females with vWD eventually resort to hysterectomy to stop the severe menorrhagia.

Hemophilia. Hemophilia occurs in 1 in 5000 males and is caused by genes at the long-arm tip of the X chromosome. Hemophilia A is deficiency of Factor VIII, while Hemophilia B is deficiency of Factor IX.[36] Normal plasma levels of F VIII and F IX are 50%-150%. Hemophilia can be divided into three levels of severity: mild, moderate, and severe. *Mild* hemophilia is defined by a factor level over 5% and represents 20% in contrast to *moderate* hemophilia with levels of 1%-5% (15% of cases) and *severe* with factor levels under 1% (65% of cases). Mild hemophilia may not be diagnosed until adolescence.

DUB and Coagulation Disorders. Table 5 lists laboratory tests useful

TABLE 5. Laboratory screening for severe menorrhagia

A. Initial screening
1. Complete blood count with differential; hCG testing
2. Platelet function analysis (PFA) (has replaced the old bleeding time test)
3. Fibrinogen
4. Bleeding studies
a. Prothrombin time (PT)
b. Activated partial thromboplastin time (aPTT)
B. Secondary screening*
1. von Willebrand's factor antigen
2. Factor VIII activity
3. Factor XI antigen
4. Ristocetin C cofactor
5. Platelet aggregation studies

*Severe or prolonged bleeding, menorrhagia with menarche, abnormal first tests.

for screening adolescent females with severe menorrhagia in which a coagulation disorder must be considered as part of the differential diagnosis.[1,9,36,40] Coagulation disorder prevalence in those with severe menorrhagia varies in published studies, depending on the population being studied. In one study of 1410 high school females, only 8 had an actual bleeding disorder diagnosis, although 37% noted heavy menses.[28]

The classic article by Claessens and Cowel in 1981 noted that 19% of those who were hospitalized because of severe menorrhagia had a coagulation disorder, while 28% had a coagulation disorder if there was severe anemia, and 45% if severe bleeding with hospitalization occurred with the first menstrual period (menarche) (versus 65% in Kadir and coworkers' 1998 study).[41,42] In Falcone and coworkers' 1994 study 3% of adolescent females with DUB were diagnosed with a coagulation disorder, 41% received blood transfusions, 93% improved with hormonal treatment, and 8% were managed with a dilation and curettage (D and C).[43]

Severe menstrual bleeding was reported in one study of 102 females with vWD (versus 88 controls) in 74% of those with vWD versus 6% of the controls.[44] Those with vWD have a higher incidence of menorrhagia, severe bleeding postpartum, migraine headaches, and arthritis. Such a negative impact of vWD is noted in other studies. For example, one report studied type 1 vWD patients using a patient survey of 99 patients (81 still menstruating) with mild disease versus 150 controls. In this study, those with vWD had a statistically increased history of anemia, number of tampons or towels used in menses, number with stained clothes due to menses, and birth-related bleeding that required blood transfusions.[39] In the group with vWD, there was a reduced quality of life (QOL) due to

TABLE 6. Quality of life for 99 patients with inherited bleeding disorders[42]

39% had cut down on time at work and other activity due to menses
47% felt they accomplished less during menses than they would like
38% felt they were limited in work
40% needed extra effort in work
51% had moderate, severe, or very severe dysmenorrhea

increased bleeding problems. Only 50% reported hormonal management that was effective; 17% reported that a D and C was needed, and 13% had hysterectomy.[39]

In another study of 116 females with inherited bleeding disorders (IBD) versus 69 controls, 66 had vWD (74% with menorrhagia), 30 were carriers of hemophilia (57% with menorrhagia), and 20 had Factor XI deficiency (59% with menorrhagia). Twenty-nine percent of the controls who did not have IBD had menorrhagia.[45,46] There was no association between the blood loss degree (as measured by the Pictoral Blood Assessment Chart) and disease severity in hemophilia or Factor XI deficiency. The degree of blood loss could not be predicted based on the vW factor activity (vWF:Ac).[45,46]

The duration of the menstrual period increases significantly in females with IBD, in contrast to those without IBD; there is an increase in menstrual flooding in those with IBD, but no difference in clot passage is reported. In those with IBD, 47% had seen their clinician because of the excessive menstrual bleeding, 36% received hormonal therapy due to menorrhagia, and 27% received surgery (such as D and C or hysterectomy).[45] Also reported was that the use of the Pictoral Blood Assessment Chart is not reliable for assessing blood loss.[45]

One study looked at the QOL in 99 with IBD in contrast to 69 controls that utilized a questionnaire asking about daily activities, general health, dysmenorrhea, and QOL during menstruation.[42] In this study, there were 57 with vWD; 17 were Hemophilia A carriers; 7 were Hemophilia B carriers; and 18 had Factor XI deficiency. The QOL was statistically lower if menorrhagia was present in those with IBD, if menses lasted 8 or more days, and if there was menstrual flooding or passage of clots (Table 6).[42]

DUB Prognosis. DUB in adolescent females usually results from anovulatory menstruation because of immaturity of the hypothalamic-pituitary-ovarian axis.[1,47-50] Most adolescents develop regular ovulatory menses between 1 and 5 years after menarche leading to regular menstrual patterns. The classic Southam and Richart 1966 study found that if normal menstruation does not develop within 4 years of menarche, normal menstrual function will probably not develop in adult life.[51] Many

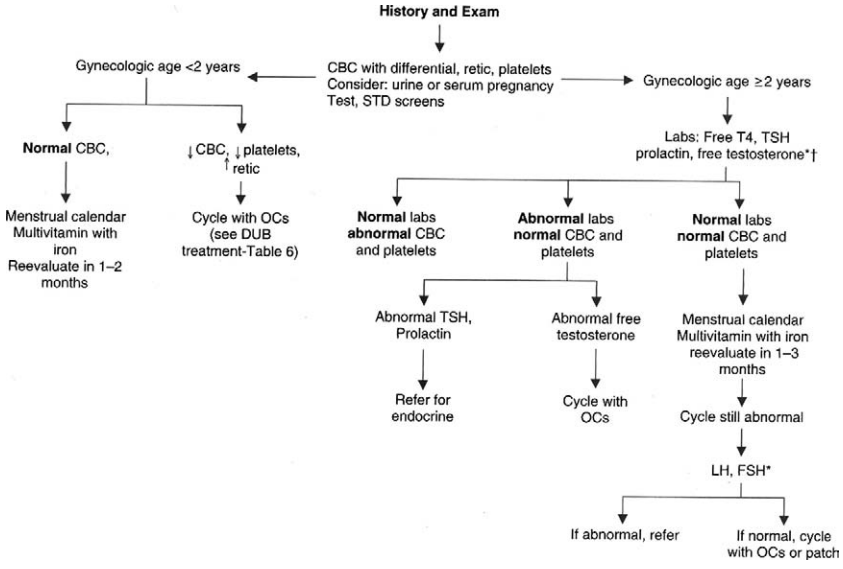

FIG 2. Evaluation of dysfunctional uterine bleeding in the adolescent. (Reprinted with permission from Joffe A, Bythe MJ. Handbook of Adolescent Medicine. Adolesc Med 2003;14(2):294.)

of these adult females had reduced reproductive potential and high rates of endometrial cancer, as there seems to be an underlying disease process causing the chronic bleeding abnormality.

DUB Management

Fig 2 outlines an evaluation process for adolescents with DUB. The management is dependent on the underlying cause and also the degree of anemia that may or may not be present; hormonal management is provided if necessary to control the abnormal bleeding.[7] *Mild* anemia is defined as a hematocrit between >33% and <36% or a hemoglobin >11 g/dL but <12 g/dL. *Moderate* anemia is defined by a hematocrit between 27% and 33% or hemoglobin between 9 g/dL and 11 g/dL. *Severe* anemia refers to a condition with a hematocrit <27% or a hemoglobin <9 g/dL or rapidly dropping. Management of DUB in adolescent females due to anovulatory menstruation is now discussed.

Absence of Anemia or Mild Anemia. Reassurance and watchful waiting is usually recommended in situations of anovulatory DUB if the patient is not overly concerned and there is no or only mild anemia. A menstrual calendar can be kept by the youth to better follow her menstrual patterns. Iron supplementation can be prescribed for mild anemia, such as ferrous

TABLE 7. Adverse effects of iron supplementation

Black stools
Constipation (add stool softener to prevent)
Diarrhea
Nausea and emesis
Worsening ulcers/colitis

TABLE 8. Thromboxane production

(1) Arachidonic acid → Endoperoxides
(2) Endoperoxides → Thromboxane A_2 → Thromboxane B_2 (Platelets)
(3) Endoperoxides → Prostacyclin (PGI_2)
(4) Vasoconstrictor
(5) Facilitates platelet clumping

sulfate at 300 mg three times a day; side effects of adding iron are noted in Table 7.[1,6] Constipation from iron supplementation may be prevented by adding a stool softener and a low release form of iron may lower the overall side effects. A 30%-50% reduction may be seen if nonsteroidal anti-inflammatory drugs (NSAIDs) are given at menses because of a direct endometrial effect on the balance of thromboxane A2 (potent vasoconstrictor) and prostaglandin I_2 (vasodilator). *Thromboxane* is a member of family of lipids called *Eicosanoids* that are produced in platelets (Table 8).

Oral or transdermal contraception (pills or patch) can also be an option to improve the DUB (especially if the adolescent is sexually active and it prevents unwanted pregnancy at the same time).[52-54] Instead of using oral contraceptives, some clinicians prescribe oral equine estrogen (2.5 mg for 21-25 days); 10 mg medroxyprogesterone acetate is then added over the last 7 days of the cycle. An alternative is to use oral progesterone for the last 10 days of the menstrual cycle to prevent the effects of unopposed estrogen and allow endometrial stabilization; a regular sloughing of the endometrium then occurs as progesterone is withdrawn.[55] Adverse effects of cyclic oral progestin therapy include bloating, increased acne, hyperphagia with weight gain, and ineffective contraception. Alternatives used by some include a natural progestin or progesterone developed from wild yams or a finely ground or miconized form (Prometrium) used to avoid or reduce side effects, although there is no underlying research for their use.[1]

Depo-medroxy-progesterone acetate (DMPA; Depo-Provera) is not typically recommended for youth with DUB because it may cause irregular bleeding that may later evolve into amenorrhea. As it is given in

TABLE 9. Schedule of oral contraceptives to control moderate to severe DUB

1. Four times a day (with an anti-emetic) until the bleeding stops
2. Three times a day for 4 days
3. Twice a day for 2 to 3 weeks
4. Allow a controlled withdrawal bleed
5. Start the oral contraceptive and oral iron supplements at once a day for 3 to 6 months

TABLE 10. DUB control with progesterone-only agents

A. Medroxy-progesterone acetate (MPA)
1. 10 mg q 4 hours, then QID 4 days, TID 3 days, BID 14 days
2. High dose may be necessary: 40-80 mg per day or 100 mg Depo IM/day
B. Norethindrone acetate (Aygestin)
1. 10 mg q 4 hours, then q 6-8 to 12 hours; taper as bleeding decreases
2. May stay on 5 mg q 12 hours for months if necessary (as teen with aplastic anemia and low platelet count)
3. 0.35 mg OD—BID for breakthrough bleeding
C. Megestrol acetate (80 mg BID may be needed)

an intramuscular form, it should not be a first option in those with a coagulation disorder. However, DMPA may be provided in unique situations, such as a sexually active female with DUB and systemic lupus erythematosus who is on coumadin.[56] Side effects of DMPA include weight gain, decreased bone mineral density, worsening of depression, protracted ovarian suppression, and hair loss.

Moderate Anemia. DUB that induces moderate anemia may be controlled with an oral contraceptive pill with 30-35 μg ethinyl estradiol.[6,52,57] As noted previously, estrogen controls menstrual bleeding by binding to endometrial receptors, stimulating specific growth factors, and producing vasculature stabilization; estrogen stimulates the development of the glands, stroma, and spiral arterioles in the endometrium. The oral contraceptive (OCP) can be given in a dose of two to four pills a day, until the bleeding is stopped and then gradually tapered over 2 to 3 weeks (Table 9). The OCP can be stopped to allow withdrawal bleeding and then be added again as a once-a-day pattern for 3 to 6 months, allow menstrual regulation and improvement of the anemia with iron supplementation. Increased estrogen may lead to nausea and emesis, thus necessitating the addition of an anti-emetic agent.

Table 10 lists various oral progesterone-only patterns that are preferred by some clinicians; high doses may be necessary to induce endometrial atrophy and estrogen is added for several days to prevent unwanted endometrial breakthrough bleeding when progesterone-only medications

TABLE 11. Control of DUB in inherited coagulation disorders

1. Factor replacement therapy
2. Intranasal DDAVP
3. Antifibrinolytics
4. Oral contraceptives
5. Levonorgestrel-releasing IUD (Mirena)

are used. As noted before, iron supplementation can be given for 3-6 months to correct depleted iron stores and a stool softener added to prevent constipation.

Severe Anemia. If severe anemia has developed as a result of DUB, emergency management may be necessary that includes provision of intravenous fluids and blood products. Intravenous Premarin (conjugated equine estrogens) is given by some at a dose of 25 mg every 4 hours; two doses are usually effective in 75% of patients and only two to four doses are usually needed because of the hemostasis that results because of direct clotting effects with increased production of fibrinogen, Factor V and Factor IX activity, and increased aggregation of platelets. Many clinicians will not use intravenous estrogen because it is not usually needed and because of the increased risk for thromboembolism that may be present when high doses of estrogen are used. An anti-emetic agent must be added to offset the estrogen-induced nausea and emesis. A progesterone is added to allow a regulated menstrual bleeding.

Instead of intravenous estrogen, many clinicians use oral contraceptives as outlined in Table 9. Fortunately, such hormonal management is effective in controlling DUB in over 90% of such situations. If these measures are ineffective, other causes must be considered, such as coagulation disorders.[9,43] Other medications can be added, such as Desmopressin acetate or antifibrinolytics, as considered in the next section.

Management of DUB Due to Coagulation Disorders

Factor Replacement Therapy

Table 11 lists methods of DUB management in patients with coagulation disorders.[1,6,58,59] Control of menstrual bleeding is based on working with the delicate balance between thrombosis and bleeding. Hemostasis physiology involves the three following basic phases: *vascular* phase (blood vessel vasoconstriction), *platelet* phase (the primary hemostatic mechanism involving platelet plug formation), and the *fibrin thrombus formation* phase.[60] The basis of management is factor replacement

TABLE 12. Side effects of intranasal DDAVP

1. Facial flushing (asymptomatic)
2. Thrombosis (rare)
3. Hyponatremia (more common in children, if given repeatedly, or too much fluid)
4. Headaches
5. Nausea
6. Weakness

therapy involving either Factor VIII, Factor IX, or vW factor, in which factor levels should be at 30% or more for minor bleeding and 100% for major bleeding as noted with surgery or intracranial hemorrhage. Recombinant factor concentrates are preferred if available; otherwise, pathogen-safe plasma-derived concentrates are used. NSAIDs are not effective in reducing blood loss in those with inherited bleeding disorders.

Intranasal DDAVP

The treatment of choice is intranasal DDAVP (Desmopressin acetate; 1-deamino-8-*d*-arginine vasopressin) since it raises plasma concentrations of Factor VIII and vWF 2- to 6-fold by way of endogenous release of these factors. Intranasal DDAVP is best for those with Type 1 vWD with normal vWF available from storage sites; however, it can also help with menorrhagia in those with mild hemophilia and other vW types.[36,38]

The following three forms of DDAVP are available: intranasal, subcutaneous, and intravenous. Concentrated intranasal DDAVP (Stimate) is made as a 1.5 mg/mL preparation with two-thirds the effect of the intravenous form and the formulation used to treat diabetes insipidus should not be used for patients with coagulation disorders and menorrhagia. A dose of 300 μg (two metered doses) is used for those over 50 kg and the patient is then observed for 60 to 90 minutes after giving the medication. Side effects of intranasal DDAVP are listed in Table 12 and include mild fluid restriction necessitating monitoring of the urinary output and daily weights for urinary retention. If the intravenous form of DDAVP is used, the dose is 0.3 μg/kg given in 25-50 mL normal saline over 15-20 minutes; peak action occurs in 30 to 60 minutes.

Antifibrinolytics

Antifibrinolytics (ie, epsilon aminocaproic acid (Amicar) or tranexamic acid) are also used as adjunctive management for menorrhagia in hemophilia, as well for mucosal bleeding (epistaxis, dental extraction, oral bleeding).[25,36,38] Antifibrinolytics improve coagulation by preventing clot degradation in areas high in fibrinolytic activity, in inhibiting

TABLE 13. Side effects of antifibrinolytics

1. Nausea and emesis
2. Headaches
3. Abdominal pain
4. Avoid with urinary tract bleeding due to potential for intrarenal clots

fibrinolysis, and by preventing change of plasminogen to plasmin. They can be taken along with DDAVP, factor replacement therapy, and coagulation Factor IX concentrates. Antifibrinolytics should not be taken immediately with prothrombin-complex concentrates because of increased risk for clot formation; however, they can be taken 4-6 hours after prothrombin-complex concentrates are stopped. Side effects of antifibrinolytics are noted in Table 13.

Tranexamic acid (Cyklokapron) improves menorrhagia by significant lowering of plasminogen activator activity and plasmin activity in menstrual fluid. It is used in Europe and given orally at a dose of 20-25 mg/kg every 6-8 hours orally (maximum: 1.5 g) or at an intravenous dose of 10 mg/kg every 8 hours (maximum: 1 g); the intravenous form is used in United States. *Epsilon aminocaproic acid (Amicar)* is prescribed as oral medication (flavored syrup or tablets) at a dose of 50-100 mg/kg every 6 hours (maximum: 24 g/d). Gastrointestinal side effects are increased at higher doses.

Oral Contraceptives

Females with DUB and inherited bleeding conditions can also be treated with OCPs since they raise Factor VIII activity (FVIII:Ac) in hemophilia carriers and in vWD patients. OCPs ameliorate hemostatic deficiencies, raise Factor VIII/vWF-ristocetin cofactor activity, and ameliorate prolonged bleeding time.[39,45,52,61] The benefits and risks of using estrogen must be considered when prescribing oral contraceptives; for example, some will use estrogen for females with a history of deep vein thrombosis if taking coumadin.[56,62]

Levonorgestrel-releasing Intrauterine Device

The levonorgestrel-releasing intrauterine device (IUD; Mirena IUD or Mirena coil) releases a small dose of levonorgestrel that has a number of effects and benefits, as listed in Table 14.[38,56,63,64] One of the benefits is improvement of DUB in females with coagulation disorders, although its historic link to pelvic inflammatory disease has limited its use in adolescent females.[52,56,62]

TABLE 14. Effects and benefits of levonorgestrel IUD

A. Contraceptive effects
- Prevents fertilization
- Interferes with ovum development
- Interferes with sperm movement and ability to penetrate ovum
- Inhibits sperm survival
- Helps prevent egg release
- Thickens cervical mucus

B. Benefits
- Effective contraception for 5 years
- Eventual reduction in menstrual flow
- OK for those with coagulation disorders
- Up to a 90% reduction in bleeding
- 20%-50% with no menses after 1 year
- Good for those with mental retardation/developmental disorders
- Frequent amenorrhea
- Decreased dysmenorrhea
- Decreased premenstrual syndrome
- Very low rates of infectious complications

Other Management Options

Various other options have been used in adult females to control irregular menstrual bleeding, including danocrine (Danazol), GnRH agonists (buserelin, leuprolide [Depo Lupron], nafarelin [Synarel]), D & C (dilation and curettage), and hysterectomy.[38,65] Danocrine is a synthetic hormone prescribed to manage endometriosis, breast cysts, and heavy menstrual bleeding in adult females. Danocrine suppresses estrogen and prevents menstruation, although it is teratogenic and can lead to masculinization. It has limited research support in adolescents. Also with limited research data in adolescents is the use of GnRH agonists used in adult females to stop ovulation.

Amenorrhea

Amenorrhea or absence of menstrual flow is divided into *primary* and *secondary* amenorrhea.[66,67] *Primary* amenorrhea is defined as lack of menstruation by age 14 at sexual maturity rating (Tanner Stage) 1 (having no sexual maturation) or by age 16 with some sexual maturation; lack of menses 3-4 years after thelarche may also be considered to be primary amenorrhea.[1] Primary amenorrhea has a prevalence of 3 per 100 adolescents in the United States. *Secondary* amenorrhea points to menses cessation for at least 4 to 6 months after regular menses has been established or for a time equal to a total of three or more previous

TABLE 15. Causes of primary amenorrhea

- Hypothalamic-induced
  - Stress
  - Drugs
  - Exercise
  - GnRH deficiency
  - Obesity
  - Eating disorders
  - Others
- Pituitary-induced: hypopituitarism
  - Congenital (idiopathic)
  - Head trauma
  - Tumor (prolactinoma)
  - Others (as hemochromatosis)
- Ovarian-induced
  - Gonadal dysgenesis
  - Polycystic ovary syndrome (PCOS)
  - Tumor
  - Resistant ovary syndrome
  - Others
  - Ovarian failure
    - Radiation or chemotherapy-induced
    - Premature failure
    - Autoimmune oophoritis
- Others
  - Adrenal gland tumor
  - Congenital adrenal hyperplasia (complete or partial)
  - Androgen insensitivity syndrome (AIS)
  - True hermaphroditism
  - Hyperthyroidism or hypothyroidism
  - Uterine synechiae
  - Pregnancy
  - Vaginal agenesis
  - Transverse or longitudinal vaginal septum that obstruct the outflow
  - Imperforate hymen
  - Cervical agenesis
  - Others

menstrual cycles. Oligomenorrhea (Table 1) is defined as menses that occur at intervals over 45 days and are usually irregular as well. Causes of amenorrhea and oligomenorrhea are the same in most cases and are now considered in the next section.

Primary Amenorrhea

Etiology. Table 15 lists causes of primary amenorrhea and includes physiologic delay (constitutional growth delay), chronic illness, Turner's syndrome (gonadal dysgenesis), Mayer-Rokitansky-Küster-Hauser syndrome (MRKH syndrome), and androgen insensitivity syndrome.[1,6,68-71]

TABLE 16. Clinical classification of amenorrhea in the adolescent*

I. Primary amenorrhea with pubertal (sex) delay
  A. Gonadal malformation
    1. Turner syndrome (gonadal dysgenesis)
    2. Testicular feminization syndrome (androgen insensitivity syndrome)
  B. Hypothalamic-pituitary dysfunction
    1. Physiologic delay (most common)
    2. Functional disorders: hypothalamic-induced:
      —such as weight loss, eating disorders, exercise, stress, others
    3. Organic disorders: prolactinoma, chronic illness, others
II. Primary amenorrhea without pubertal (sex) delay
  A. Pseudoamenorrhea
    1. Imperforate hymen
    2. Transverse vaginal septum
  B. Mayer-Rokitansky-Kuster-Hauser Syndrome
    —agenesis of vagina, cervix, uterus
  C. Polycystic ovary syndrome (hyperandrogenemia syndromes)
  D. Chronic illness (including thyroid disorders)
  F. Others
III. Secondary amenorrhea
  1. Pregnancy (most common)
  2. Hypothalamic-induced
    —such as weight loss, eating disorders, exercise, stress
  3. Polycystic ovary syndrome (hyperandrogenemia syndromes)
  4. Thyroid disorders
  5. Pituitary disorders (pituitary adenoma)
  6. Hypoestrogenemia (ovarian dysfunction or ovarian hypofunction)
  7. Chronic illness
  8. Others

*Modified and reprinted with permission from Greydanus DE, Patel DR. The female athlete: before and beyond puberty. Pediatr Clin North Am 2002;49:553-80.

The most common cause is physiologic delay. Primary amenorrhea can be seen in those with hirsutism and virilization, such as seen in polycystic ovary syndrome (PCOS), mixed gonadal dysgenesis, gonadal dysgenesis with virilization, congenital adrenal hyperplasia, ovarian or adrenal tumors, true hermaphroditism, and others (Table 15).

Table 16 lists causes of primary amenorrhea based on those with pubertal delay and those without pubertal delay. Causes of primary amenorrhea that do not usually cause secondary amenorrhea are included in Table 17. However, there is considerable overlap between disorders that cause primary versus secondary amenorrhea and a careful evaluation is necessary for both. Table 18 lists causes of hirsutism and virilization in females, while Table 19 lists disorders to be distinguished from hyperandrogenism.

Medical History. Menarche typically occurs 2-3 years after thelarche with a range of 1 to 5 years, often between Tanner stage 3 and 4; however,

TABLE 17. Causes of primary amenorrhea and not secondary amenorrhea

Androgen insensitivity syndrome
Congenital hydrocephalus
Idiopathic hypopituitarism
Kallmann's syndrome
Laurence-Moon-Bardet-Biedl syndrome
Hermaphroditism
Mayer-Rokitansky-Kuster-Hauser syndrome (genital tract agenesis)

approximately 15% occur in Tanner stage 5. Menarche often occurs within a year of the mother's menarche. Key questions to explore in an adolescent female presenting with amenorrhea is whether pregnancy may have occurred (even if "primary" amenorrhea is being investigated), if there is normal or low estrogen state, if there is evidence of excess androgen production, and if there is an anatomically normal genital tract. The medical history should review pubertal development carefully and look for evidence of congenital anomalies, hernia as an infant, systemic illnesses, excessive exercise patterns, and virilization (ie, hirsutism, clitoromegaly, scalp hair thinning, severe acne).

A careful history of the menstrual pattern is important to obtain, to distinguish primary from secondary amenorrhea.[1] What is the sexual history of the patient, looking for previous pregnancies or abortions? What is the state of the patient's nutrition? Is there a history of endometrial destruction from a D and C (Asherman's syndrome) or stenosis of the cervix from previous vigorous cautery because of an abnormal Pap smear? Is there a history of drug abuse, since various drugs can lead to amenorrhea, including cocaine, oral contraceptives, progestin-only pills, calcium channel blockers, cimetidine, phenothiazines, tricyclic antidepressants, metoclopramide, and others.

Physical Examination. A careful physical examination is important, looking for tall stature (46,XY karyotype), short stature (46,X0 in Turner's syndrome), hypertension (with delayed sexual maturation as in 17-α-hydroxylase deficiency), bradycardia (as in hypothyroidism or anorexia nervosa), anosmia (Kallmann's syndrome), visual field defects with papilledema (brain tumor), or cachexia (anorexia nervosa).[1,6]

A careful gynecologic examination is important in identifying the cause of primary amenorrhea. The breast examination may reveal small, pale areolae (as in anorexia nervosa) or chronic estrogen decrease (as in Turner's syndrome or other causes of ovarian failure). If amenorrhea is present with galactorrhea, consider a prolactin-producing pituitary adenoma. The presence of sparse or absent public hair with full breast

TABLE 18. Causes of hirsutism and virilization in females*

- Increased androgen-dependent hair and virilism
  - Genetic and familial increased androgen sensitivity
  - Androgen excess
    - "Psychogenic" hirsutism
    - Stress
    - Schizophrenia
  - Exogenous androgens
    - Medical
      - Hypoplastic anemias
      - Growth stimulation
      - Adrenal replacement
      - Danazol
      - Synthetic progestins in oral contraceptives
      - Adrenocorticotropic hormone (ACTH) therapy
    - Nonmedical
      - Bodybuilding and athletic anabolic steroids
      - Female to male transsexualism
    - Environmental (?)
      - Skin contact with male using topical testosterone
      - Anabolic steroids given to livestock
      - Plant or microorganism androgens
  - Adrenal androgens
    - Congenital adrenal hyperplasias
      - 21-hydroxylase deficiency
        - Classic
        - Late-onset
      - 3β-hydroxysteroid dehydrogenase deficiency
        - Classic
        - Late-onset
      - 11β-hydroxylase deficiency
        - Classic
        - Late-onset
    - Adrenal tumors
      - Adrenocortical carcinoma
      - Testosterone-secreting adenoma
      - Adrenal rest adenoma and carcinoma
    - Cushing's disease
  - Ovarian androgens
    - Polycystic ovary syndrome (PCOS)
      - Conditions associated with PCOS
        - PCOS with ovarian tumor
    - Pineal gland hyperplasia and diabetes
    - Congenital lipoatrophic diabetes
    - Hyperprolactinemia
    - Hyperthyroidism
    - Hypothyroidism
    - Androgen-secreting cysts and hyperplasias
      - Stromal hyperplasia and hypertheocosis
      - Solitary follicle cyst
      - Hyperreaction luteinalis of pregnancy

TABLE 18. Continued . . .

Androgen-secreting ovarian tumors
Arrhenoblastoma (androblastoma)
Thecoma-fibroma group tumors
Granulosa cell tumors
Lipoid cell tumors
Gynandroblastoma
Epithelial tumor
Luteoma of pregnancy
Testicular androgens in XY females
5α-reductase deficiency
Mixed gonadal dysgenesis
True hermaphroditism
17β-hydroxysteroid dehydrogenase deficiency
Other rare intersex conditions

*Reprinted from Greydanus DE, Shearin RB. Adolescent sexuality and gynecology. Philadelphia, PA: Lea & Febiger, 1990:176.

development suggests androgen insensitivity syndrome with a 46,XY karyotype. Hirsutism, severe acne, enlarged clitoris, and scalp hair thinning (frontotemporal) in the youth suggest excess androgen production.

The external genitalia should be examined, looking for an enlarged clitoris (androgen excess), an abnormal hymen (imperforate or cribriform), or evidence of estrogen deficiency (thin, pink, vulvar mucosae). The cervical mucus should be checked and evaluated by the *Vaginal Cytological Maturation Index* (Table 20). If there is copious, watery mucus that reveals spinnbarkeit by ferning an air-dried slide using microscopy, this suggests a high-estrogen state as noted in the late proliferative state before ovulation. A thick and tenacious cervical mucus that dries in amorphous clumps without ferning on microscopy suggests a progestin effect as seen in the secretory state after ovulation, after pregnancy, or due to a progestin-containing pill.

A transverse vaginal septum and presence of cervix should be examined during the pelvic examination. If there is a history of primary amenorrhea, vaginal patency should be established with moistened cotton or Dacron-tipped applicator or a moistened gloved finger. If a bimanual exam is possible, look for a mass (consider pregnancy or hematometra); also look for ovarian enlargement, as in polycystic ovary syndrome. A rectal exam may be necessary to help establish the presence of a cervix or to find a mass proximal to an obstructed vaginal canal (as in a hematocolpos).

Detection of anatomical genital defects results from genital inspection and pelvic/rectal examination. A karyotype is often needed in cases of primary amenorrhea. Definitive procedures include sonography, magnetic

TABLE 19. Disorders to be distinguished from hyperandrogenism*

- Hirsutism
  - Generalized hypertrichosis
    - Idopathic
    - Familial
    - Drugs and toxins
      - Diphenylhydantoin
      - Minoxidil
      - Diazoxide
      - Phenothiazines
      - Cyclosporine
      - Hexachlorobenzene poisoning
      - Streptomycin
      - Penicillamine
      - Cobalt
      - Acrodynia
      - Danazol
    - Rare genetic syndromes
      - Hypertrichosis lanuginosa or universalis
      - Hepatic and erythropoietic porphyrias
      - Laurence-Moon-Biedl syndrome
      - Morgagni-Stewart-Morel syndrome
      - Seckel bird-headed dwarfism
      - Cornelia de Lange's syndrome
      - Trisomy E
      - Hurler's syndrome
    - Chronic systemic illness
      - Chronic renal failure
      - Dermatomyositis
      - Cancer
    - Chronic central nervous system dysfunction
      - Cerebral palsy
      - Spina bifida
      - Multiple sclerosis
      - Postencephalitic states
      - Others
    - Endocrine Disorders
      - Hypothyroidism
      - Growth hormone-secreting pituitary adenoma
      - Hyperprolactinemia
    - Chronic malnutrition
      - Anorexia nervosa
  - Localized hirsutism or hypertrichosis
    - Hairy nevus (several types)
    - Broken extremity bone
    - Extremity lymphedema
    - Repeated local trauma
  - Clitoromegaly without ambiguity
    - Clitoral priapism
    - Fibroma of clitoris
    - Chronic vulvovaginitis

TABLE 19. Continued . . .

Acne
Cushing's syndrome
Exogenous exacerbating agents
Androgenic steroids
Synthetic progestins
Glucocorticoids
Lithium
Diphenylhydantoin
Barbiturates
Isoniazid
Rifampin
Iodides
Kelp and other seaweed
Bromides
Persistent unpleasant body odor without apparent disease
Foreign body (especially in the nose or vagina)
Genetic disorders of organic acid metabolism
Trimethylaminuria
Dietary spices
Poor hygiene

*Reprinted from Greydanus DE, Shearin RB. Adolescent Sexuality and Gynecology. Philadelphia, PA: Lea & Febiger, 1990:177.

TABLE 20. Vaginal cytological maturation index

1. Use Pap smear fixative for the vaginal smear
2. One point is given for each superficial cell, [1/2] point for each intermediate cell, and 0 points for each parabasal cell.
3. A score >40 suggests some estrogen effect
4. A score of 50-60 is found in pubertal females
5. 0-30 is seen in prepubertal females
6. 31-55 reflects a hypoestrogenic state of adult females.

resonance imaging (MRI), and laparoscopy. The patient should be screened for additional or associated congenital anomalies if a genital anomaly is present; these include musculoskeletal, cardiac, and/or renal anomalies in some cases. Endocrinological and gynecological consultation is often necessary for those with primary amenorrhea. Tables 21 and 22 outline basic laboratory testing for adolescents with amenorrhea.

MRKH Syndrome. The MRKH syndrome (Table 22) or Müllerian agenesis is a congenital condition in which there is absence of all or part of the uterus and vagina as the cause of primary amenorrhea.[1] Typically there is uterine agenesis (or rudimentary uterine development) with absence of the upper two-thirds of the vagina in association with the presence of ovaries, fallopian tubes, breasts, pubic hair, normal female

TABLE 21. Laboratory testing for amenorrhea in adolescents (to be used selectively after thorough clinical examination)

Pregnancy test
Hormonal investigation:
LH and FSH: Increased in ovarian failure/dysgenesis; normal or decreased in others
Thyroid hormone levels
Prolactin levels
If virilization/hirsutism present: DHEAS, LH/FSH ratio (nl: <2.5:1), testosterone (total and free)
Level of estradiol and progesterone and/or
Vaginal smear to evaluate for epithelial cell estrogenization
Pelvic ultrasound to define anatomy (uterus hypoplasia)
Vaginoscopy
Bone age
Chromosome evaluation
Anti-ovarian antibodies
Head CT/MRI
Pelvic/abdominal MRI
Renal ultrasound/IVP
Laparoscopy

hormonal patterns, and a normal female karyotype (46,XX). Over half may have urinary tract anomalies, while 25% have vertebral column malformations. The differential diagnosis includes the androgen insensitivity syndrome (Table 22) and confirmatory diagnostic tests include the pelvic ultrasound, MRI, and laparoscopy.

Other Vaginal Outflow Tract Abnormalities. The female with an *imperforate hymen* is noted in 1 in 1000 and presents with primary amenorrhea and cyclic pelvic pain. There is a bulging, bluish hymenal membrane and even retrograde menses that may predispose to endometriosis. Management involves early diagnosis with incision and drainage of the imperforate hymen under anesthesia.[72,73] *Transverse vaginal sepum* is noted in 1 in 80,000 and the obstruction is due to a septum at the junction of the upper and middle thirds of the vagina. Retrograde menstruation may occur, leading to endometriosis. A similar problem can occur with *longitudinal vaginal septum*, when the septum is attached to the vaginal wall on the side of the cervix, thus obstructing outflow.

Others. In male pseudohermaphroditism there is a 46,XY karyotype and a female phenotype with uterovaginal atresia and functioning testicular tissue. Leydig cell agenesis occurs due to defective LH receptors and this leads to inadequate androgen secretion. Various autosomal-recessive disorders are noted with ambiguous genitalia. In *17-α-hydroxylase deficiency*, there is an individual with a female phenotype that has breast tissue, primary amenorrhea, and often, hypertension.

In the *androgen insensitivity syndrome* (formerly called the testicular feminization syndrome), the individual has a female phenotype with full breast development and scant or absent pubic and axillary hair. The vagina ends in a blind pouch and testes are present. There is typically a history of a herniorraphy as an infant. There is also an increased level of LH, testosterone, and estradiol; this individual is at increased risk for a gonadal neoplasm, although this risk is lower than that seen in 46,XY gonadal dysgenesis.

Secondary Amenorrhea

The most common underlying cause of secondary amenorrhea (after pregnancy) in an adolescent is anovulation, resulting from inhibition of FSH and LH because of various factors that influence the hypothalamus (Table 22).[1,6,9,69,74] This "hypothalamic" amenorrhea can be due to major weight loss or gain, increased stress, systemic illness, excessive physical activity as noted in competitive sports, and others. Secretion of steroid and neuroendocrine hormones can resemble patterns noted in early puberty or even prepuberty with low gonadotropin levels and reduced sex hormones (androgens and estrogen).

Other factors inducing amenorrhea include pregnancy, immaturity, thyroid disorders (hyper- or hypothyroidism), polycystic ovarian disorder, anorexia nervosa (even before severe weight loss develops), other chronic illnesses, various medications, illicit drugs, prolactinoma, pituitary destruction from infiltration or infarction, Asherman's syndrome (uterine synechiae), and others (Table 22).

As noted, overlap and confusion between causes of primary versus secondary amenorrhea may occur, since both can be due to dysfunction of the hypothalamic-pituitary-ovarian axis. The history of previous menstruation suggests the presence of a patent uterus and vagina, thus eliminating the diagnosis of a congenital anatomic disorder of the uterus and/or vagina (ie, MRKH syndrome). Causes of secondary amenorrhea and oligomenorrhea are essentially the same. Table 23 provides a suggested plan for evaluating the cause of secondary amenorrhea (Table 23; Fig 3). Table 24 provides a plan for evaluation of an ovarian versus adrenal etiology in an adolescent with hyperandrogenism and oligomenorrhea or amenorrhea.

Perplexing causes of amenorrhea in youth may require consultation with experts in endocrinology, gynecology, or neurology. Management depends on the underlying cause and is reviewed below. If transient hypothalamic suppression is found, reassurance and patience is the usual recommendation. It is important to consider various factors that influence

TABLE 22. Gynecological disorders of adolescent females*

Gynecologic Disorder	Special Comments	Differential Diagnosis	Laboratory Testing
Amenorrhea (primary)	Physiologic is the main cause; MRKH syndrome associated with renal abnormalities and spinal malformations; short stature with delayed sexual maturation: Turner syndrome; delayed sexual maturation + hypertension seen in 17α-hydroxylase deficiency; Swyer syndrome; absence of smell sense suggests Kallmann syndrome; visual field deficits suggests brain tumor	Physiologic Imperforate hymen Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome Turner syndrome (45,XO and mosaicism) Chronic illness Hypothalamic: Stress, eating disorders, exercise, depression; androgen insensitivity syndrome (46,XY); Swyer syndrome; others: see text	Serum gonadotropins (FSH, LH), prolactin, TSH Pelvic Ultrasound MRI Head CT/MRI Renal ultrasound/IVP (intravenous pyelogram) Karyotype Laparoscopy
Amenorrhea (secondary)	Pregnancy is the main cause: history of sexual activity-may present with a midline "pelvic mass"; causes of oligomenorrhea and secondary amenorrhea are essentially the same. Also important is history of dietary habits, exercise, stress; acne and hirsutism suggest elevated androgen levels; Athlete triad syndrome: amenorrhea, dysfunctional eating patterns, osteopenia-porosis	Pregnancy; lactation Stress Eating disorders Chronic illness Exercise-induced Prolactinoma (headaches, visual field deficits, galactorrhea) PCOS (polycystic ovary syndrome); see text	Pregnancy test (β-hCG) Progesterone challenge Serum estrogen, FSH, LH Bone mineral densitometry Serum prolactin Thyroid screen Head CT
Dysmenorrhea (primary)	Pelvic pain during normal ovulatory menstruation; no underlying pelvic pathology. May also see gastrointestinal symptoms, headache, myalgia, sweating.	Physiologic	
Dysmenorrhea (secondary)	May be seen at menarche or 3+ years postmenarche.	Endometriosis Pelvic inflammatory disease Reproductive tract anomalies Pelvic adhesions Cervical stenosis Ovarian masses Pelvic congestion syndrome Rule out urinary tract or gastrointestinal causes	Laparoscopy STD screen Pelvic Ultrasound MRI
Dysfunctional uterine bleeding (DUB)	Menstrual calendar useful to get accurate history of menstrual pattern; get sexual activity history; establish presence/absence of ovulation: basal body temperature charts, serum progesterone, urinary luteinizing hormone (LH), and possibly endometrial biopsy; rule out an STD; virilization evaluation necessary if hirsutism present.	Anovulatory bleeding; pregnancy, ectopic pregnancy; coagulation disorders (as von Willebrand disease, others), anatomic lesions, endometrial pathology; cervicitis or cervical dysplasia; pelvic inflammatory disease; ovarian cysts; polycystic ovary syndrome; severe stress, rapid or severe weight gain or loss, drug abuse; see text	CBC, platelets, beta-HCG, Pap smear, PT, PTT, bleeding time, other coagulation disorders screening; D-21 progesterone; thyroid screen; STD screen; ultrasound (transvaginal; pelvic), MRI; hysteroscopy
Ectopic pregnancy	Pain with history of secondary amenorrhea, often with vaginal bleeding.	See DUB differential	β-hCG; pelvic ultrasound

TABLE 22. Continued . . .

Gynecologic Disorder	Special Comments	Differential Diagnosis	Laboratory Testing
Endometriosis	Presentation in adolescence not the same as in adults. May have acyclic pain, abnormal uterine bleeding, GI symptomatology	See secondary dysmenorrhea	Laparoscopy Laparotomy
Mittelschmertz	Pain associated with ovulation in the middle of a menstrual cycle. May last 1-3 days and be mild to severe.	See primary dysmenorrhea	Menstrual calendar
Ovarian masses	Presents with a lateral location; abnormal menses	Ovarian cysts Ovarian tumors (benign, malignant) Polycystic ovary syndrome Ectopic pregnancy Tubo-ovarian mass	Pregnancy test Pelvic ultrasound
Pelvic inflammatory disease	STD that can lead to uterine tenderness, adnexal tenderness, tenderness on cervical motion, mucopurulent vaginal or cervical discharge; can see fever ($T > 101°F$, 38.3°C); polymicrobial disorder of the upper genital tract often precipitated by *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, others (*Gardnerella vaginalis*, *Mycoplasma hominis*, *Ureaplasma urealyticum*, *Haemophilus influenzae*, coliforms, cytomegalovirus, peptostreptococcus, and other anaerobes). Can involve various combinations of endometritis, salpingitis, tubo-ovarian abscess, and pelvic peritonitis. Complications include infertility, chronic pelvic pain, ectopic pregnancy.	Ectopic pregnancy Appendicitis Pyelonephritis Ovarian cyst Septic abortion Others	Nonspecific: white blood cells on saline prep; elevated ESR; elevated CRP; lab evidence of *Neisseria gonorrhoeae* or *Chlamydia trachomatis* Specific criteria: positive biopsy; endometrium showing endometritis; evidence of PID on laparoscopy; ultrasound or MRI showing that fallopian tubes are thick and filled with fluid; may be free fluid in the pelvis or a tubo-ovarian complex
Polycystic ovary syndrome (PCOS; hyperandrogenemia syndrome)	Insulin resistance with hyperinsulinemia, hyperandrogenemia, and chronic anovulation; can see irregular menses (secondary amenorrhea, oligomenorrhea, DUB), hirsutism, possible virilization, variable obesity, acanthosis nigricans, possible bilateral enlarged ovaries.	Other causes of hyperandrogenism; HAIR-AN syndrome; congenital adrenal hyperplasia (11β-hydroxylase, 21-hydroxylase, 3β-hydroxysteroid dehydrogenase deficiency); Cushing's disease, hyperprolactinemia; ovarian or adrenal tumor; mixed gonadal dysgenesis (45X/46XY, 45X/46XX/46XY); gonadal dysgensis with virilization; true hermaphroditism	LH, FSH, T-4, prolactin, testosterone (total and free), insulin level; lipid profile; dehydroepiandrosterone sulfate (DHEAS); 17-hydroxyprogesterone; 24-hour urine for free cortisol; dexamethasone suppression test; pelvic ultrasound
Premenstrual syndrome (PMS)	Variety of symptoms start before and end with menses	Premenstrual dysphoric disorder (PMDD); depression; anxiety; others, depending on the presenting symptoms; see text	DSM-IV (2000) criteria for PMDD

Abbreviations: CBC, complete blood count; Pap, Papanicolaou smear; STD, sexually transmitted disease; MRI, magnetic resonance imaging; GI, gastrointestinal; ESR, erythrocyte sedimentation rate; HAIR-AN, hyperandrogenism, hirsutism, insulin resistance, acanthosis nigricans; DSM-IV, Diagnostic Statistical Manual-4th Edition (American Psychiatric Association); PT, prothrombin time; PTT, partial thromboplastin time.

*Reprinted, with permission, from Greydanus DE, Feingerg AN, Patel DR, Homnick DN, eds. The Pediatric Diagnostic Examination. New York, NY: McGraw-Hill Medical Publishers, 2008:743-748.

TABLE 23. Plan for evaluation of secondary amenorrhea

1. Pregnancy should always be considered and ruled out, even with denial of sexual activity and history of only one late or absent menstrual period.
2. The state of estrogenization should be determined and if estrogen priming of the endometrium is occurring using the vaginal cytologic maturation index (Table 20) Look at microscopic evidence of fern ing (denoting anovulation) in an air-dried slide of cervical mucus.
3. Consider a *progestin challenge*. If there is no pregnancy or chronic illness present, give medroxyprogesterone acetate, 10-20 mg/day PO, for 5 days, or a single dose of progesterone-in-oil, 100 mg IM. If a withdrawal bleeding occurs, this suggests the hypothalamus-pituitary axis is able to respond, at least to some extent, there is an endometrium, and the genital outflow tract is patent. The usual situation is either hypothalamic suppression or reversible chronic anovulation. Mild hypoestrogenism is suggested by a scant bleeding, while no bleeding at all suggests such conditions as outflow-tract agenesis or obstruction, loss of the endometrium, ovarian failure, or chronic hypoestrogenism from various causes. The presence of chronic hypoestrogenism implies the need for estrogen replacement. If there is a nonresponse along with the presence of normal or low FSH, this suggests major dysfunction of the hypothalamic-pituitary axis.
4. If the patient has normal estrogenization and normal withdrawal bleeding with the progestin challenge, the patient and parents can be reassured that the reproductive tract is normal. Help her deal with such underlying factors as stress, extreme exercise, major weight gain or loss, and others. If the rest of the evaluation is normal, one can adapt a “watch and wait” process in which the patient is seen periodically (as every 3-6 months) to await the resumption of normal menstruation. A repeat or periodic progestin challenge test may be helpful in select situations; it may also prevent endometrial proliferation secondary to unopposed estrogen that may lead to dysfunctional uterine bleeding (as menometrorrhagia). Oral contraceptives may be used without fear that they will delay the resumption of normal menstruation when stopped. Oral contraceptives can also be used to manage dysfunctional uterine bleeding if this develops.
5. Oligomenorrhea is a common process in adolescent females and extensive evaluation is not usually needed in an otherwise healthy patient who is within 2 years of her menarche. Specific evaluation may proceed, however, if the oligomenorrhea continues over 2 years from menarche, develops for over 6 months in a youth with previous normal menses, or if the initial evaluation suggests an underlying chronic illness.
6. If the cause of the amenorrhea or oligomenorrhea is not clear after the above evaluation, a more extensive evaluation is necessary looking for various medical conditions and/or mental health issues (ie, stress) that starts with a full history and complete physical examination. The evaluation includes pelvic and rectal exams looking for potential anatomical or physiologic disorders. It is very important to identify the presence or absence of uterine or adnexal mass(es). A pelvic ultrasound and MRI may be necessary to confirm normal or abnormal anatomy while important laboratory data supportive of the evaluation are noted in Table 21. A head CT or MRI may be needed to rule out a CNS tumor especially if galactorrhea or various neurological signs are present.

TABLE 23. Continued . . .

7. Look for hyper/hypothyroidism and galactorrhea. An abnormal TSH screen should prompt further evaluation for thyroid dysfunction that can lead to altered menstrual status. Increased prolactin levels suggest hyperprolactinemia as the cause of the menstrual dysfunction, although increased prolactin can also be seen in hypothyroidism, hirsutism, and PCOS as well. Fasting prolactin levels can be increased without galactorrhea being present. Prolactin levels over 50-100 ng/ mL warrant a head MRI or CT to screen for a prolactinoma. Prolactin levels over 70 mg/ mL are typically seen with amenorrhea, although screening for chronic renal failure should also be done. Low levels of serum prolactin in cases of amenorrhea are consistent with hypothalamic disorder induced by stress.
8. It is also important to evaluate this patient with secondary amenorrhea for dysfunction of the hypothalamic-pituitary-ovarian axis. An FSH and LH level can be obtained for performing the progestin challenge test, although some clinicians will not perform this screen unless there is no withdrawal bleed after the progestin is given. Since the added progestin can suppress the gonadotropins, one should wait at least 7 to 10 days after the progestin challenge test to screen for levels of FSH and LH. If the FSH is over 40 mIU/L and the LH is over 25 mIU/L, this indicates a hypergonadotropic condition suggesting the presence of ovarian failure essentially in proportion to the degree of FSH/LH increase; further evaluation is necessary, as reviewed below. It is also important to obtain a karyotype in these patients, looking for such conditions as 46,XY or 45,X or 45,X/46,XX. If a 46,XY karyotype is found, perform a laparoscopy while an autoimmune disease evaluation is important to pursue if 45,X/46,XX is found (46,XY could be the diagnosis in primary, not secondary amenorrhea). It is often difficult to separate low from normal FSH/LH levels, particularly in young adolescents. However, low or normal gonadotropin levels in the presence of a normal progestin challenge suggest a diagnosis of reversible hypothalamic dysfunction with anovulation, due to stress or early PCOS. Gonadotropin levels that are unmeasurable suggest irreversible deficiency of the hypothalamus or the pituitary. Low or normal gonadotropin levels in the presence or absence of a withdrawal bleed suggest an underlying endocrinologic disorder of either hypothalamic or pituitary origin. Consider PCOS if the LH is increased and the FSH is normal or low; however, in some PCOS, the LH is also normal. An elevated LH in contrast to the FSH level is also found in hyperestrogenism. If the patient with amenorrhea has normal estrogen status, this suggests that the ovaries are functional. Low estrogen levels are consistent with ovarian failure if there is also high FSH/LH or pituitary deficiency with low FSH/LH. If hypothalamic dysfunction occurs, the estradiol levels may be near the lower margin of normal with low FSH/LH levels. Estradiol levels can be mildly increased or normal in PCOS or other conditions of hyperandrogenism. If hirsutism is noted, screening for hyperandrogen states is necessary, as reviewed elsewhere.
9. If oligomenorrhea or amenorrhea develops in the presence of a hyperandrogenic state, evaluate for an ovarian versus adrenal etiology, as reviewed in Table 24.

menses (Table 25). If systemic disorders (including endocrine conditions) or tumors are found, again, referral to appropriate specialists is needed. PCOS is reviewed below. If there is primary failure of the ovaries, hormonal replacement is needed, as reviewed below. Comment is now provided on specific medical causes of amenorrhea.

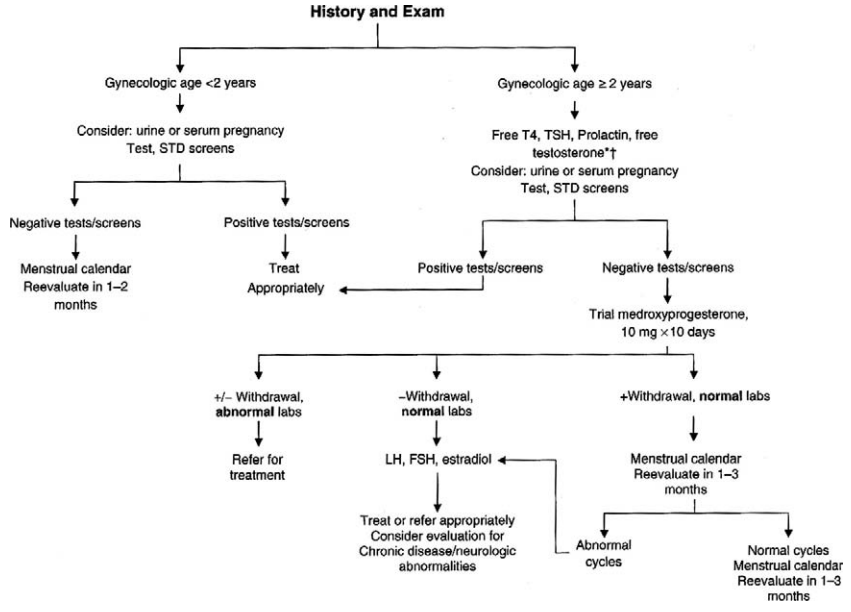

FIG 3. Evaluation of secondary amenorrhea and oligomenorrhea in the adolescent. (Reprinted with permission from Joffe A, Bythe MJ. Handbook of Adolescent Medicine. Adolesc Med 2003;14(2):294.)

Hypothalamic Amenorrhea. Hypothalamic disorders causing amenorrhea include constitutional growth delay, congenital GnRH deficiency, and hypothalamic amenorrhea.[1,9] Congenital GnRH deficiency can be seen in the Kallman syndrome with hypogonadism and anosmia. Hypothalamic amenorrhea results from such causes as psychological stress, poor nutrition, chronic illness, and strenuous exercise. The amenorrhea is due to disruption of GnRH pulsatile release that leads to reduced levels of FSH, LH, estradiol, and prolactin along with hypercortisolism. Stress that can induce amenorrhea can include depression, anxiety, and illicit drug use or withdrawal from drug use. Pseudocyesis (false pregnancy) is an extreme example in which LH and prolactin secretion are high enough to sustain luteal function and even galactorrhea. The inhibition of hypothalamic neuroendocrine function seen in systemic illness (Table 26) is similar to that described in starvation along with additive factors of stress and altered steroid metabolism.

Menstrual dysfunction may be seen in female adolescents with obesity because of chronic anovulation. The underlying mechanisms of the oligomenorrhea and secondary amenorrhea include increased estrogen

TABLE 24. Evaluation of ovarian versus adrenal etiology in an adolescent with hyperandrogenism and oligomenorrhea or amenorrhea*

Measure the serum or plasma testosterone, free testosterone, and androstenedione.
- In functional ovarian or adrenal hyperandrogenism, the total testosterone may be normal but the free testosterone and androstenedione are increased. If the total testosterone is over 200 ng/dL, suspect an ovarian or adrenal virilizing tumor and obtain imaging studies.

Measure the DHEAS. If the levels are over 600 μ/dL, suspect an adrenal tumor and obtain imaging studies.

If the etiology remains unclear, obtain a dexamethasone suppression test, using an oral dose of 1 mg/m^2 daily in divided doses for 5-7 days. Measure the plasma-free testosterone, DHEAS, and cortisol both before and after administration:
- Suspect *PCOS* if the free testosterone is not suppressed, but the cortisol and DHEAS are.
- If neither the free testosterone nor the cortisol is suppressed, consider an adrenal virillizing tumor, Cushing's syndrome, or noncompliance.
- If the free testosterone is normally suppressed, then obtain an ACTH stimulation test to rule out congenital adrenal hyperplasia (CAH).

Abbreviations: DHEAS, dihydroepiandrosterone sulfate; PCOS, polycystic ovary syndrome; ACTH, adrenocorticotropic hormone.

*Reprinted, with permission, from Greydanus DE. Breast and gynecological disorders. In: Hofmann AD, Greydanus DE, eds. Adolescent Medicine, 3rd ed. Stamford, CT: Appleton & Lange, 1997:541.

TABLE 25. Influences on the menstrual cycle

Age
Weight and height
Physiologic and sex development
Psychological stress
Nutritional deficiencies
Genetic predisposition
Percentage body fat
Amount of exercise
Chronic illness
Medications (prescription or over the counter)
Race
Others

levels because of aromatization of androgens from excess adipose tissue; in addition, there is complex interplay of hyperinsulinism and hyperandrogenism, more characteristically seen in PCOS, but seen to some extent in obesity. Stress, noted in some with obesity, can also contribute to menstrual disruption. Anovulation and obesity can also be secondary to underlying hypothalamic disruption seen in the Prader-Willi syndrome or hypothyroidism. If the obese individual has no underlying medical illnesses, weight loss can lead to restoration of menstruation.

TABLE 26. Chronic illnesses that induce hypothalamic amenorrhea

Cancer (including chemotherapy and radiation)
Celiac disease
Chronic renal failure
Cystic fibrosis
Diabetes mellitus (poorly controlled)
Inflammatory bowel disease (Growth issues and amenorrhea may arise before bowel symptoms)
Sarcoidosis
Sickle cell disease
Systemic lupus erythematosus (other rheumatoid disorders)
Thyroid disease
Tuberculosis
Other systemic illnesses

Anorexia Nervosa. Menstrual irregularities can develop in females with eating disorders, such as anorexia nervosa and bulimia nervosa.[1,9,75-77] Amenorrhea may develop with or precede significant weight loss in the female with anorexia nervosa and menstruation may not return until after the weight has been normalized. Estrogen deficiency along with low calcium dietary intake often lead to osteopenia or even osteoporosis in these patients. Given that adolescence is the age during which peak bone mass is acquired, there may be severe consequences for future bone health. Bone densitometry should always be part of the evaluation; calcium supplementation and in some cases OCPs can be used until weight normalization and stabilization (see text below on the female athlete triad).[78]

Other Hypothalamic and Pituitary Disorders. Hypogonadotropic anovulatory amenorrhea can develop because of hypothalamic destruction by infarction, tumor infiltration, or trauma.[1,9] Although amenorrhea may be the initial or presenting complaint, neurological symptoms and/or evidence of other hormone deficiencies may be seen, together with low levels of gonadotropins (FSH, LH) and end-organ hormones (estrogen, testosterone). Signs of estrogen deficiency are typically less evident than that seen with primary ovarian failure.

If gonadotropins are very low (ie, $<$10 IU/L), image the sella turcica to look for a lesion of the anterior pituitary or hypothalamus causing the amenorrhea. Trauma or tumor can cause disruption of the pituitary stalk resulting in pubertal disruption including growth delay; if this occurs after puberty is finalized, findings include amenorrhea, galactorrhea, diabetes insipidus, hypoadrenalism, and hypothyroidism. The most common tumor that is involved is a *craniopharyngioma* that can present with headaches,

TABLE 27. Features of Turner syndrome*

Short stature (usually does not exceed 142 cm)
Sexual infantilism with streak ovaries (may have slight amount of pubic hair)
Turner facies (fish mouth, low-set ears, malformed ear lobes, epicanthal folds, micrognathia)
Short, webbed neck with low hairline
Cubitus valgus (wide carrying angle of forearm)
Fingernail anomalies
Shield chest with broadly spaced, hypoplastic nipples
Abnormal hearing and vision (including color blindness)
Cardiovascular disorders (hypertension, coarctation of the aorta, aortic stenosis, bicuspid aortic valve)
Various renal anomalies
Multiple pigmented nevi
Associated with recurrent otitis media, diabetes mellitus, chronic lymphocytic thyroiditis
Features in infancy: short birth length, lymphedema of hands and feet, loose posterior neck folds
Hirsutism if component of the Y-chromosome is present

*Reprinted, with permission, from Greydanus DE. breast and gynecological disorders. In: Hofmann AD, Greydanus DE, eds. Adolescent Medicine, 3rd ed. Stamford, CT: Appleton & Lange, 1997:339.

visual field defects, and dysfunction of the hypothalamus. A head MRI or computed tomography will identity the tumor.

The most common infiltrative disorders of the hypothalamic-pituitary area are central nervous system leukemia and histiocytosis X; others include tuberculosis, sarcoidosis, head trauma, hemochromatosis, and postpartum necrosis. With the exception of craniopharyngiomas, intraspinal tumors cause headaches and abnormal neurological findings more often than they do amenorrhea. Also, craniospinal irradiation for cancer can lead to hypothalamic-pituitary dysfunction. The empty sella syndrome has rarely been noted in adolescents. Prolactin levels should be measured in chronic menstrual dysfunction, especially if galactorrhea develops. Prolactin secretion disorders are noted in 15% of adult females with amenorrhea, and the degree of elevated prolactin is associated with the degree of menstrual dysfunction. Prolactin levels over 70 ng/L are associated with amenorrhea, although the amenorrhea is not related to the presence or severity of galactorrhea.

Primary and Secondary Ovarian Failure. Increased FSH and LH levels are noted in hypergonadotropic hypogonadism as reflected in the ovarian failure of gonadal dysgenesis (Turner syndrome),[79-82] effects of radiation or chemotherapy, and autoimmune oophoritis.[1,3,9] Approximately 25% of females with primary amenorrhea have gonadal dysgenesis. Those with the 45,XO karyotype have classic features, including

short stature and hypoestrogenism with failure of secondary sexual development (Table 27). The 45,X/46,XX karyotype may have few somatic defects other than short stature, and their ovaries may allow ovulation and pregnancy prior to ovarian failure.

The development of amenorrhea and loss of estrogenization after a few or some menstrual cycles also occurs in ovarian failure due to irradiation or chemotherapy (ie, vincristine, cyclophosphamide, others) for management of cancer and also in the rare situation of premature menopause. The combination of both chemotherapy and radiation is especially toxic to ovarian function. Premature menopause may occur as a feature of an autoimmune, multiple endocrine syndrome with antiovarian antibodies or even as an isolated disorder. It may also be seen in resistant ovary syndrome, as well as with various collagen vascular disorders or autoimmune endocrinopathies, such as diabetes mellitus, myasthenia gravis, hyperparathyroidism, thyroiditis, Addison disease, pernicious anemia, or vitiligo. Management of ovarian failure includes hormone replacement (estrogen and progesterone) along with counseling about self-image, infertility, and sexual functioning.[81,82]

Endocrine Disorders. Excessive production or major deficiency of the major hormones may lead to significant disruption of the complex menstrual cycle because of either interference with neuroendocrine feedback and/or negative impact on the overall health of the adolescent female.[1,3,9] This hypothalamic dysfunction can lead to anovulation with dysfunctional uterine bleeding or amenorrhea. Thus, menstrual dysfunction can be seen in such endocrine disorders as hyperthyroidism, hypothyroidism, Addison disease, Cushing syndrome, late-onset congenital adrenal hyperplasia (21-hydroxylase deficiency), hyperprolactinemia, Prader-Willi syndrome, Laurence-Mood-Biedl syndrome, and others.

Amenorrhea is typically seen with hypothyroidism, while DUB is often noted with hyperthyroidism. Hyperpigmented skin folds and pressure areas are seen in Addison disease and vitiligo is found with ovarian autoimmune disease. Acanthosis nigricans reflects insulin resistance and androgen excess is seen with anovulation and menstrual dysfunction; the latter is noted with PCOS (see next section). Menstrual dysfunction can also be seen with pituitary adenomas. If growth hormone excess starts in childhood, an acromegalic tall stature results and later onset leads to acromegalic features of enlarged jaws and digits; acromegaly is typically seen with hyperprolactinemia. Rare tumors of the ovary or liver can produce human chorionic gonadotropin leading to menstrual dysfunction.

Polycystic Ovary Syndrome

PCOS Pathophysiology. PCOS (PCO; hyperandrogenemia syndrome; old term: Stein-Leventhal syndrome) is a hyperestrogenic, hyperandrogenic state of anovulation found in 5%-10% of adolescent and adult females, representing 30% of adult women with chronic amenorrhea and 75% with chronic oligomenorrhea (Table 22).[1,6,83-87] The underlying pathophysiology of PCOS is chronic dysfunction of hypothalamic stimulation of the pituitary, pituitary stimulation of the ovaries, and steroid feedback to the hypothalamus. There seems to be an increase in GnRH that induces the pituitary to increase LH secretion (both basal levels and pulse amplitude), either as a cause of or as a result of androgen synthesis from the ovaries.

Hyperinsulinemia is part of PCOS and may also induce increased LH secretion.[88] PCOS patients, whether obese or not, have increased levels of insulin in comparison to controls. The state of insulin resistance found in PCOS patients leads to a state of hyperinsulinism that induces increased androgens in hyperandrogenic females but not normal females. There is resistance to the normal hypoglycemic effect of insulin. This resistance is found in muscle and adipose tissue, but not in liver tissue.

When puberty begins, the anterior pituitary reacts to increased estrogen levels by increasing LH levels and decreasing FSH production that lead to abnormal stimulation of ovarian-derived estradiol and androgens as well as abnormal maturation of ovarian follicles and a state of chronic anovulation. The anovulation leads to the prevention of cyclical progesterone secretion. Since there is less FSH secretion, antral follicular development is dysfunctional, oocyte degeneration increases, and ovulation does not occur.

There is excess secretion of androgens that is mainly ovarian. In normal situations, progesterone is changed in the ovaries to 17-α-hydroxyprogesterone and then to androstenedione in ovarian theca cells by 17-α-hydroxylase and 17,20-lyase. This androstenedione is converted to testosterone in theca cells and then estradiol in granulosa cells. In addition, PCOS patients have a congenital defect of cytochrome P45c17α that leads to an increase in 17-α-hydroxylase and some increase in 17,20-lyase (desmolase) action causing an increase of testosterone concentration in the ovaries. Many PCOS patients also have decreased production and levels of sex steroid binding globulin, thus allowing for higher free testosterone levels even if the total testosterone is normal. There is also heightened androgen production from the adrenal glands along with heightened peripheral production of estrone from androgens in

TABLE 28. Laboratory test results in PCOS patients

LH: Mild increase in levels
FSH: Low limits of normal
LH-FSH ratio: >2.5:1
Estradiol: moderate increase in levels
17-hydroxyprogesterone: mild increased levels
Prolactin: mild increase
Androgen: mild to moderate increase in levels
—Free and total testosterone
—Dehydroepiandrosterone sulfate (DHEAS) (can be normal)
—Androstenedione
—Early morning urinary 17-ketosteroids
Sex hormone-binding globulin (SHBG): decreased
Hyperinsulinemia (fasting levels of glucose/insulin ratio <4.5)
Abnormal lipid profile
—Increased cholesterol
—Increased low-density lipoprotein
—Increased very-low density lipoprotein
—Reduced high-density lipoprotein
—Increased triglycerides

adipose tissue, leading to increased steroid levels in PCOS patients. Premature atresia of follicles and anovulation result from elevated testosterone levels. The elevated estrone levels stimulate GnRH from the hypothalamus leading to increased LH levels and androgen secretion. Testosterone and androstenedione are metabolized to a potent androgen, DHT (5-α-dihydrotestosterone), in the skin.

The result of PCOS pathophysiology is a chronic state of high androgen and estrogen levels, stimulating an increased but acyclical production of GnRH from the hypothalamus that causes a dysfunctional cycle of anovulation and hyperandrogenism. Such a PCOS pathophysiologic state can also occur because of an underlying state of elevated adrenal androgen production, as in Cushing's syndrome or congenital adrenal hyperplasia, some ovarian tumors, or dysfunctional release of GnRH from the hypothalamus because of other conditions.

PCOS Symptomatology. Variable PCOS features (Table 28) may arise in females as or after puberty begins, including amenorrhea or irregular menstrual bleeding from anovulation, hirsutism, acne, and obesity. Hyperandrogenism is reflected by hirsutism (measured with the Ferriman-Gallway scale) in over 60%, acne vulgaris in 25%, and male-pattern alopecia in some PCOS patients.[1,6,67,89,90] Virilization may occur as reflected in clitoromegaly (over 5 mm in diameter), voice deepening, and abnormal fat-muscle distribution. There may be premature adrenarche. At puberty, the patient may be overweight for height and even overtly obese.

Acanthosis nigricans (velvety, hyperpigmented areas, especially in the axilla, neck, and back) may reflect hyperinsulinemia, often associated with obesity.[91] The family history may be positive for PCOS, diabetes mellitus, hyperinsulinism, hirsutism, infertility, and/or adrenal enzyme deficiency.

The term, PCOS, represents a spectrum of hyperinsulinemia syndrome and an adolescent with PCOS may not have all the classic PCOS features found in adult females. Adolescents with PCOS may have one or two classic features along with suggestive laboratory findings (see next section) and later progress to other PCOS features. For example, there may not be overt obesity or enlarged ovaries until adulthood. Eventually the ovaries become enlarged with a thickened capsule that contains many small follicular cysts with theca interna hyperplasia ("string of pearls") that is seen on an ultrasound examination. In adults obesity is noted in over 50% but ovulation may occur in 10%-20% and as many as one-quarter may have regular menstrual cycles. Overt diabetes mellitus (type 2) may develop in some PCOS patients.

PCOS Laboratory Studies. Classic laboratory results in PCOS patients are listed in Tables 22 and 28. The combination of an increased LH-FSH ratio (>2.5:1) with increased free testosterone and androstenedione levels is suggestive of PCOS. A pelvic examination, pelvic ultrasound, or laparoscopy may identify polycystic and sometimes enlarged ovaries (bilateral); however, the ultrasound in adolescents with PCOS may be nonspecific and normal females may have the appearance of "polycystic" ovaries.

The diagnosis of PCOS in young adolescents may be difficult and subtle based on general symptomatology along with an increase in androgens, estradiol (can be normal), a high LH-FSH ratio (>2.5:1), with or without ultrasound confirmation of polycystic ovaries. A diagnosis of PCOS may be made if two of these three criteria are present: oligomenorrhea and/or anovulation, hyperandrogenism (clinical or biochemical evidence), and ultrasound evidence of polycystic ovaries).[92] This is an expansion (Rotterdam criteria) of a National Institutes of Health conference in 1990 that defined PCOS as a disorder with hyperandrogenism and/or hyperandrogenemia, oligomenorrhea, and exclusion of known disorders.[93] The exact definition with specific criteria remains controversial, especially for adolescents.[1,93]

If there is a rapid onset of hirsutism or virilization with high levels of testosterone (>150-200 ng/dL), DHEAS (>700 μ/dL), and androstendione (>500 mg/dL), consider an adrenal tumor as the diagnosis. Polycystic ovaries can be seen with Cushing disease, congenital adrenal hyperplasia (including some partial enzyme deficiencies), hyperprolactinemia,

TABLE 29. Management options for PCOS patients

Oral progesterone
Oral contraceptives (also transdermal or transvaginal hormonal contraceptives)
Spironolactone (androgen receptor antagonist)
Flutamide (androgen receptor antagonist)
Metformin
Electrolysis and thermolysis for hair removal
Obesity management
Acne vulgaris management
Ovulation induction (not often used in adolescents)
—Clomiphene citrate
—GnRH agonistic analogs (leuprolide acetate or nafarelin)
—Ovarian wedge resection
Laser "drilling" of the ovary (decrease ovarian stromal steroids by reducing the amount of stroma)
Management of additional endocrinopathies

and HAIR-AN syndrome. The HAIR-AN syndrome is a variant of PCOS with hirsutism, insulin resistance, acanthosis nigricans, and androgenization; these patients can also develop impaired glucose metabolism and hyperlipidemia.[1,3,9,94]

PCOS Management. Table 29 lists management options for adolescents with PCOS.[95-100] If hirsutism is not noted and the adolescent female is not sexually active needing contraception, 10 mg of medroxyprogesterone (Provera) can be prescribed for 12-14 days each month, to induce withdrawal bleeding. Oral contraceptives (estrogen-dominant) can also be used in combination with an anti-androgen medication (as spironolactone or cimetidine) to reduce clinical signs of androgen excess (as hirsutism or acne if present) and allow more clinically normal menstrual periods.[1,6] The regular use of contraceptive steroids (pill or patch) provides management of the anovulation and unopposed estrogen stimulation of the endometrium found in patients with PCOS. Hormonal contraceptives can also suppress hyperandrogenism and increase the production of sex steroid binding globulin, thus helping prevent more hirsutism development.

Hirsutism is also managed with androgen receptor antagonists as spironolactone (50-100 mg twice daily) or flutamide, another anti-androgen medication that inhibits androgen uptake.[1,6,101-104] Other anti-androgen agents have been used, such as cyproterone acetate (Cyprostat). Metformin (Glucophage) reduces serum insulin levels, decreases ovarian cytochrome P450c17α activity, and improves hyperandrogenism in obese PCOS patients.[98,99] Other medications used with type 2 diabetes mellitus have been used as well, including pioglitazone (Actos) and rosiglitazone

TABLE 30. Methods to evaluate hypoestrogenemia in adolescents

Physical and sex development (delay of sex development)
Vaginal maturation index (VMI)
Vaginal smear to evaluate for epithelial cell estrogenization
Serum estradiol level
Body weight
Bone mineral densitometry

(Avandia). Future sequelae of adolescent PCOS may include infertility, endometrial carcinoma, diabetes mellitus (type 2), hyperlipidemia, and cardiovascular disease.[1,9] However, early intervention with alteration of dietary habits, physical exercise, and androgen suppression therapy can minimize adult morbidity. Diet intervention is considered most important as fresh vegetables, fruit, and high-fiber nutrition can reduce weight, as well as metabolic consequences of PCOS.

Amenorrhea in Adolescent Athletes

Irregular menstruation (ie, amenorrhea and oligomenorrhea) is often seen in females with strenuous exercise patterns, involving 10%-15% of female athletes overall and two-thirds of the top female athletes.[105-111] *Primary* amenorrhea can also be seen as well, with a 5-month menarcheal delay noted for each year of strenuous exercise in the prepubertal period.[112] S*econdary* amenorrhea is well-known in females engaged in such sports as ballet, cycling, gymnastics, and distance running.[108] Irregular menses is described in 12% of swimmers and cyclists, 20% of females involved in excessive exercise in general, 44% of ballet dancers, and 51% of endurance runners.[108]

As noted in Table 25 there are many factors that influence menstrual cycles. Low body fat is not the only cause of menstrual irregularity and former statements that menses cannot occur below a body fat percentage of 17% have not been proven. A female athlete with amenorrhea can be at the same body fat level as one with regular menses.[109] A major cause of lack of menstrual periods in athletes involved in excessive exercise patterns is the resultant hypothalamic amenorrhea or oligomenorrhea induced by dysfunction of GnRH production and LH pulsivity.[108]

The strenuous exercise pattern of these athletes leads to a significant drain of energy that their relatively low caloric intake cannot correct, to sustain normal menses.[109] Other factors may be involved as well, such as stress, positive family history of irregular menses, chronic illness, and others. A thorough search for other factors influencing menses is important, before concluding that the athlete's menstrual dysfunction is

mainly due to intense exercise patterns. As noted before, the investigation should include congenital anomalies, short stature, hypoestrogenemia (Table 30), galactorrhea, virilization, and others.[1,108-110,113]

The combination of amenorrhea, dysfunctional eating patterns, and osteopenia or osteoporosis seen in some female athletes has been termed the *Female Athlete Triad* by the American College of Sports Medicine.[113] Various combinations of these three components can be seen in female athletes, especially those whose sport emphasizes a thin or even prepubertal physique that can be threatened by the normal changes of puberty. The need for thinness can lead to unhealthy intake of calories, protein, fat, and calcium. Young adolescents may develop delayed puberty with their continued prepubertal (hypoestrogenic) state, while postpubertal athletes can have chronic anovulatory amenorrhea, and oligomenorrhea with hypoestrogenism.[109,110] The low estrogen levels can prevent the development of normal peak bone mass with increased risks for osteopenia, osteoporosis, and stress fractures.

Management: Female Athlete Triad. Management of the adolescent female athlete with amenorrhea or oligomenorrhea is based on the underlying etiology of the irregular menses. If strenuous physical activity is a paramount factor, reducing the exercise pattern by 10% or more and improving nutritional intake (with calcium supplementation) will be beneficial.[108-111,114] The athlete can be educated that she is at increased risk for bone complications (ie, reduced bone marrow density, osteopenia, and osteoporosis) if the menstrual problems are part of a state of chronic hypoestrogenemia.[115] She may never develop a normal bone mineral density (BMD) if a state of chronic amenorrhea and low BMD occurs, even if later menses becomes regular.[108] Those with low BMD, and athletic occupations such as dancing, are at increased risk for stress fractures.[108]

Adolescents with the female athlete triad (ie, menstrual dysfunction and/or abnormal eating patterns) should receive daily supplementation of calcium (1000-1500 mg per day), Vitamin D (400-800 IU), vitamin B complex, and vitamin E (100-200 IU).[108-111,116] Research notes that about 50% of the required bone mass is obtained during adolescence, and it is recommended by many clinicians to provide estrogen supplementation in the form of oral contraceptives or conjugated estrogen for the purpose of seeking prevention of bone loss.[117,118] The American Academy of Pediatrics recommends avoidance of hormonal management if she is within 3 years of menarche; however, oral contraception (or other estrogen supplementation) is suggested if she is 3 years after menarche and over 16 years of age while always seeking to improve nutritional intake, provide calcium supplementation, and recommend a reduction in exercise patterns.[119]

Unfortunately, many athletes who are committed to their sport will refuse to reduce exercise schedules or alter established dietary patterns.[120] It is also important to understand that using estrogen supplementation is controversial and not proven to improve or even protect BMD with or without weight gain.[108,109,121] It is also not possible to predict the outcome in a specific athlete with the female athlete triad, in terms of the actual effects of chronic menstrual dysfunction and potential hypoestrogenemia in a specific youth.[108,120,122] Taking estrogen supplementation does not correct the underlying menstrual abnormality and once the estrogen is stopped, there is often a resumption of the previous menstrual dysfunction. Estrogen consumption can lead to a number of side effects, including nausea, emesis, breast tenderness, breast congestion, increased risk for clot potential, and others.[52,62] Some research suggests that using oral contraceptives with ethinyl estradiol under 50 μg may not prevent osteoporosis.[123] In our clinics, however, we have an overall better outcome when these patients use combined oral contraceptives without placebo for an average of 6 months, compared to those who do not use OCPs (HA Omar, unpublished observation, 2008).

Females with the most reduced BMD are those who are thin and inactive; also strenuous physical activity patterns that involve weight-bearing can lead to high mechanical forces that neutralize the potential reduced BMD effect seen with a thin physique.[108,120] Research showed that accretion of bone can be increased with weight-bearing exercise, and in some athletes with amenorrhea that results in having normal or even increased BMD; these athletes are gymnasts, runners, ice skaters, and tennis players.[108,120]

Dysmenorrhea

Primary Dysmenorrhea

General. The term, *primary dysmenorrhea*, is used to define pelvic pain that occurs during menstruation in which there is no overt pelvic pathology; *secondary dysmenorrhea* refers to pain during menstruation due to specific pelvic abnormalities, such as endometriosis or pelvic inflammatory disease (see next section).[1,6,9,124,125] The pain of primary dysmenorrhea can be *mild* (does not affect normal activity and requires only minimal analgesic help), *moderate* (some reduction in regular activity and requires regular use of analgesics), and *severe* (unable to carry out regular activities and analgesics are typically not helpful). *Severe* pain is often associated with nausea and emesis.

Primary dysmenorrhea typically begins 6 to 12 months after menarche,

although it may not be noted until the third gynecologic year after menarche. The pain usually lasts 1-3 days typically initiating with the menstrual flow or up to several hours after menses begin; sometimes it occurs several to 48 hours before the menstrual flow starts. Nearly two-thirds of ovulating females have some menstrual discomfort for 1-3 days of most ovulatory menses, with nearly half of them having mild pain, one-third having moderate pain, and 14% reporting severe pain. Primary dysmenorrhea is the most common medical cause of school or job absence and its incidence rises from the early teenage years through young adulthood and first pregnancy.

Etiology. The pain of primary dysmenorrheal menstrual cramps is due to the pathophysiology of the postovulatory period in which there is a rise and fall of progesterone that leads to the release of prostaglandins causing an increase in uterine contractions and an irritation of endometrial nerve endings.[1,6,9] The endometrium produces prostaglandins (eg, $PGF_{2\alpha}$) and leukotrienes from arachidonic acid through cyclooxygenase and lipooxygenase pathways, respectively. Reduced secretion of progesterone by the corpus luteum because of ovulation leads to a breakdown of lysosomes in endometrial cells, with a release of phospholipase A_2, which converts fatty acids (derived from cell membranes) into arachidonic acid. PGF_{2a} and leukotrienes (eg, leukotriene B_4 and leukotriene C_4) stimulate smooth muscle contractions.

There is increased resting tone of the myometrium, heightened contractions (frequency and amplitude), and increased dysrhythmic contractions. Vasoconstriction induces ischemia of tissue as well as sensitization of myometrial neuronal endings to various pain-inducing chemicals. Those with primary dysmenorrhea have increased levels of circulating prostaglandins during menstruation (compared to those without such cramps). There may also be increased sensitivity to circulatory prostaglandins and increased levels of vasopressin that can lead to increased myometrial contractions and more pain.

The reaction of individual adolescents to menstrual cramps can vary from some that are unable to continue regular activities to others that seem less affected. Also, menstrual cramps can worsen with psychological factors, such as depression or anxiety. In addition, dysmenorrhea may be aggravated by factors such as longer menstrual flow, obesity, and the copper IUD. Decreased pain may be seen with parity, regular exercise, oral contraceptives, NSAIDs, and the progesterone IUD.[1]

Symptomatology. There may be a constant ache with superimposed crampy or spasmodic pain that is bilateral and symmetrical; the pain is localized to the lower abdomen but can radiate to the lower back or

TABLE 31. Features associated with primary dysmenorrhea

Backache
Diarrhea
Dizziness
Fatigue
Flushing
General malaise
Headache
Inner thigh pain
Lightheadedness
Low abdominal pain
Muscle cramps
Nausea
Vomiting

anterior thighs. A variety of additional symptomatology may be seen, as noted in Table 31. The differential diagnosis includes secondary dysmenorrhea and pain due to genitourinary tract infections (pelvic inflammatory disease), inflammatory bowel disease, endometriosis, tumors (ovarian or uterine), and pregnancy (particularly early spontaneous miscarriage). Fig 4 provides a plan for the evaluation and treatment of dysmenorrhea.

Secondary Dysmenorrhea

Although most episodes of dysmenorrhea in adolescents represent primary dysmenorrhea, secondary dysmenorrhea can also be seen. In this case, there is an underlying organic etiology to the pain. Clues to this diagnosis include that the pain begins at menarche or 3 or more years after menarche; also, there may be pain that is not colicky or crampy. It may be associated with dysfunctional uterine bleeding or changing menstrual patterns; it is not easily relieved with medications or there is a history of pelvic surgery. Table 32 lists causes of secondary dysmenorrhea that should be considered.[1,6,9] Note that a diagnosis of a "retroverted" uterus is not a cause of secondary dysmenorrhea.

Evaluation: Medical History. A careful history is important in evaluating an adolescent who presents with what appears to be pelvic pain, seeking to distinguish primary from secondary dysmenorrhea or other nongynecological causes. Table 33 lists important points to consider in taking a medical history. *Congenital malformations* (ie, vaginal septum and other Müllerian obstructive anomalies) may present with pain because of menstrual flow obstruction; there is a history of primary amenorrhea with normal breast development, cyclic dysmenorrhea,

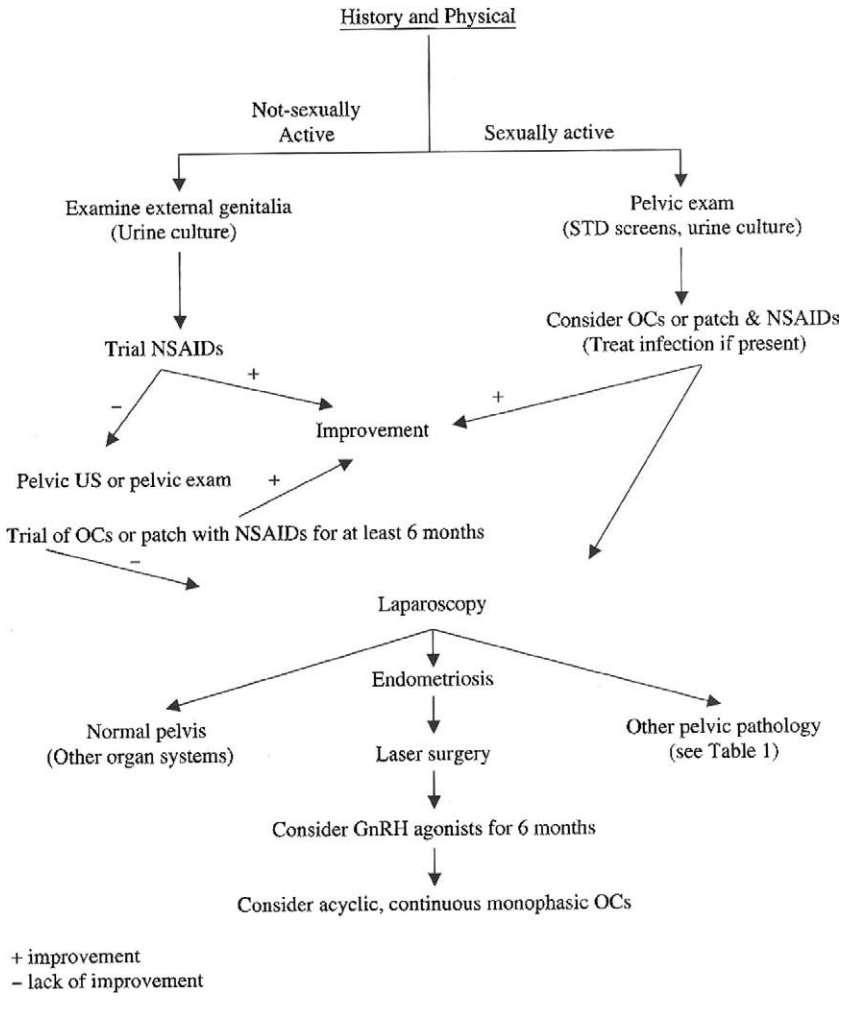

FIG 4. Dysmenorrhea. (Reprinted with permission from Blythe MJ. Common menstrual problems of adolescence. Adolesc Med 1997;8(1):107.)

and/or hematocolpos. In this situation, the pain is typically present with menarche and imaging studies allow a precise diagnosis.

Ovarian cysts may or may not be palpable and typically lead to lateralized adnexal tenderness. Fortunately, most ovarian cysts are asymptomatic and unlikely to cause pain, and finding a cyst does not necessarily implicate the cyst as causing the dysmenorrhea. Symptomatic cysts are typically follicular with such symptoms as irregular menses, urinary frequency, sensation of abdominal or pelvic heaviness, and

TABLE 32. Causes of secondary dysmenorrhea

Adhesions secondary to pelvic inflammatory disease or pelvic surgery
Anatomical genital defects (obstructing mullerian defects)
Complete cervical stenosis (with secondary amenorrhea and subsequent dysmenorrhea)
Endometriosis
Inflammatory bowel disease
Ovarian cysts
Pelvic tumors (including uterine leiomyomata)

TABLE 33. Medical history in a patient with dysmenorrhea

Age at menarche
Last time menstruation was regular (if at all)
Pain description: location, timing to menarche, menstrual flow, frequency
Severity of the pain: mild, moderate, severe (are activities disrupted?)
Do pain medications improve or relieve the pain?
Flow description (duration and quantity)
Association with systemic factors (Table 31)
Sexual history and use of any contraception
History of pregnancy (and its outcome)
History of sexually transmitted diseases
History of dyspareunia
History of other systemic disorders (ie, gastrointestinal, genitourinary, others)
History of surgical procedures
Family history of various gynecologic conditions (Table 32) (dysmenorrhea, endometriosis, ovarian cysts, infertility, virilization, cancer, others)

constipation. Complications include cyst rupture with intra-abdominal bleeding and cyst torsion. Oral contraceptives may suppress the development of ovarian cysts. Fortunately, *uterine tumors* are uncommon in adolescent females.

Worsening menstrual pain in an adolescent who is sexually active may be caused by *endometritis*. The pain is often worse during menstruation but occurs through the menstrual cycle. *Pelvic inflammatory disease* (PID)-induced menstrual pain may increase during the first 7 days of the menstrual cycle and less frequently worsen in the premenstrual period, with improvement described as the flow starts. Other evidence of PID will confirm the diagnosis, such as cervical motion tenderness, or uterine/adnexal tenderness and/or laboratory evidence of cervical infection with *Neisseria gonorrhoeae* or *Chlamydia trachomatis*.[1,6,9,126]

Pain associated with vaginal bleeding may be due to early pregnancy complications, such as *ectopic* pregnancy or *miscarriage*. Painful vaginal bleeding can also be due to gastrointestinal disorders, urologic disorders, intra-abdominal abscess, lesions of the sacrum, and orthopedic infections

TABLE 34. NSAIDs: Type I inhibitors: Carboxylic acids

1. Salicylic acid esters: aspirin
2. Acetic acids: indomethacin
3. Propionic acids: ibuprofen, naproxen, naproxen sodium, and ketoprofen
4. Fenamic acids: mefenamic acid, meclofenamate

(involving the hips and other joints). These conditions cause acute or recurrent lower abdominal or pelvic pain but not the cyclical pain of primary dysmenorrhea.

Evaluation: Physical Examination and Laboratory Testing. If the history suggests mild primary dysmenorrhea with no pain apart from the menstrual periods in an adolescent who is not sexually active, a pelvic examination is not necessary. A general examination can be done that includes an inspection of the external genitalia to rule out an imperforate hymen. If she is sexually active or if the pain is or becomes moderate or severe, a pelvic examination should be part of the physical examination process.

Laboratory testing and imaging are not usually needed for those with what appears to be mild to moderate primary dysmenorrhea that responds to basic medical management (see next section). If she is sexually active, the possibility of a sexually transmitted disease and pregnancy should be ruled out. The history and general physical examination may point to a nongynecologic cause, such as gastrointestinal, urinary, others; in such cases, appropriate testing should be done (ie, complete blood count, urinalysis, urine culture, stool for occult blood, others as appropriate).

Ultrasonography is useful to identify such conditions as a pelvic mass, pelvic abscess, adnexal torsion, ovarian cysts, pregnancy, and others. The pelvic computed tomography can be helpful if the ultrasound is indeterminate, while the pelvic MRI is more sensitive to identify Müllerian anomalies. Laparoscopy is needed to identify endometriosis or pelvic adhesions.

Primary Dysmenorrhea Management: NSAIDS. The first line of medical treatment for primary dysmenorrhea is one of the NSAIDs. NSAIDs include type I inhibitors (carboxylic acids) (Table 34) and type II (enolic acids that include pyrazolones [phenylbutazone] and oxicams [piroxicam]).[1,6,9,125] Enolic acids inhibit cyclic endoperoxide cleavage enzymes (reductase isomerase) after formation of cyclic endoperoxides as a later step in prostaglandin production. Enolic acid medications are not as effective as carboxylic acids (Table 34) and have more side effects. Thus, type I inhibitors (carboxylic acids) are the main type of NSAIDs used to manage primary dysmenorrhea.

TABLE 35. NSAIDs for the treatment of primary dysmenorrhea

Drug	Initial Dose (mg)	Maintenance Dose	Maximum Dose/24 Hours (mg)
Ibuprofen[a]	400	400 mg q4h	3200
Ketoprofen[a]	25-50	25-50 mg	300
Naproxen[a] sodium	550	q6-8h 275 mg	1375
Naproxen	500	q6-8h	1250
Mefenamic acid	500	550 mg q12h 250 mg q6-8h	Not established

[a]Available as over-the-counter drugs (ibuprofen; 200-mg tablets; ketoprofen: 12.5 mg tablets; naproxen sodium: 220-mg tablets).

Carboxylic acids suppress cyclic endoperoxide synthetase at the cyclooxygenase level and are effective medications to relieve the pain of primary dysmenorrhea. However, aspirin has limited anti-inflammatory effect on the endometrium and is not a potent reliever of menstrual cramps. Indomethacin is more effective, but its many side effects limit its use for treatment of primary dysmenorrhea; these adverse effects include gastrointestinal effects (ie, ulceration, perforation, bleeding), renal insufficiency, breast tenderness, headaches, vaginal bleeding, and others.

Thus, propionic acids (ie, ibuprofen, naproxen sodium, others) have been used because of effective relief of pain with less toxicity than the other mentioned medications; they are U.S. Food and Drug Administration approved for treatment of primary dysmenorrhea. Side effects include gastrointestinal effects and headaches. Propionic acids (Table 34) are available as over-the-counter medications. Naproxen sodium has a long half-life allowing a twice-a-day dosing. Ketoprofen inhibits prostaglandin and leukotriene synthesis, stabilizes lysosomal membranes, and has anti-bradykinin action. Dosages for propionic acids are noted in Table 35. Fenamic acids have a rapid onset of action, block myometrial receptor sites for prostaglandins that have been synthesized, inhibit 5-lipooxygenase activity (that can suppress production of leukotrienes), and can reduce heavy flow of menses. Table 35 lists basic dosage of mefenamic acid.

An NSAID (as ibuprofen, naproxen sodium, naproxen, others) is started at the onset of the menstrual flow or even before the anticipated flow onset, especially if pain precedes the bleeding. Starting the medication before the flow starts is also helpful if emesis is part of the menstrual cycle. The medication is continued for 2-4 days, depending on how the pain usually lasts. Improvement of the pain and even the amount of blood loss is noted (see section on DUB). If a propionic acid is not beneficial

after a few months' trial, the adolescent female can try mefenamic acid for a few more months' trial. Overall efficacy in partial or full relief of pain is as high as 80%. Failure of improvement may be due to the lack of prostaglandin synthetase inhibitors blocking the 5-lipooxygenase pathway that allows continued production of leukotrienes and continued dysmenorrhea.

Primary Dysmenorrhea Management: Oral Contraceptives. Oral contraceptives are also used for primary dysmenorrhea if NSAIDs are not effective and may be the first line of treatment for sexually active youth with dysmenorrhea.[1,6,9,125] Oral contraceptives prevent ovulation that in turn prevent the postovulatory high prostaglandin levels due to a corpus luteum. The lack of such high progesterone levels prevent an important step in prostaglandin production and thus lack of overt painful menstrual cramps. Added benefits include effective contraception and less menstrual flow (see DUB section). An efficacy rate of 90%-95% can be seen with the use of oral contraceptives in the management of primary dysmenorrhea. Similar results can be achieved with use of other hormonal contraceptives such as transdermal, transvaginal, injectable, and/or implantable (subdermal) methods. A combination of hormonal contraceptives and NSAIDs can also be effective. If the use of NSAIDs and/or oral contraceptives is not effective, the possibility of secondary dysmenorrhea should be reconsidered.

Primary Dysmenorrhea Management: Others. A variety of other measures may be useful in managing primary dysmenorrhea, including use of a menstrual calendar to get a clear picture of menstrual timing, reduction of sugar as well as caffeine, encouragement of adequate rest as well as regular exercise, and reduction of excess stress.[1,6,9] Psychological factors (as depression and anxiety) can worsen pain from various causes. Fish consumption containing omega-6 fatty acids (eg, salmon) can help minimize menstrual cramps. Unproven options with anecdotal testimonies of success in some adult patients include calcium channel blockers (ie, nifedipine), acupuncture, and transcutaneous electrical nerve stimulation. Side effects of nifedipine include headaches and hypotension. Education of the adolescent female about dysmenorrhea and its treatment options is important.[127]

Premenstrual Syndrome

Premenstrual syndrome (*PMS*) refers to a variety of symptoms that begin during the last part of the luteal menstrual cycle, just prior to the menstrual flow, and resolve with the onset of menstruation so that they are absent the week after menses starts.[1,6,9,128,129] PMS may begin several

TABLE 36. PMS symptomatology

Emotional features
Anecdotal reports of violence and suicide
Anger
Anxiety
Concentration difficulties
Crying
Decreased libido
Depression
Feelings of being out of control or overwhelmed
Lethargy
Mood swings
Withdrawal from usual activities
Physical features
Acne
Anorexia
Bloating
Breast tenderness or swelling
Constipation
Diarrhea
Edema
Facial puffiness
Fatigue
Headache
Increased appetite
Lower abdominal or pelvic pain
Pain: joints or muscles
Swelling of hands
Swelling of feet
Weight gain

days to 2 weeks prior to menses and the symptoms can be divided into *emotional* and *physical* features (Table 36); patients report various combinations of these features. Most females of reproductive age will note some PMS symptoms, while 3%-8% report severe enough emotional features (ie, depression, anxiety, inability to perform daily tasks) that the condition meets criteria for *Premenstrual Dysphoric Disorder* as defined by the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (1994, 2000).[130-132] Patients with premenstrual dysphoric disorder have five or more of these American Psychiatric Association criteria (ie, sadness, loss of self-worth, mood lability, anxiety, withdrawal from social relationships, anger, persistent irritability, others) in the luteal menstrual phase for at least 1 year.

PMS should be identified as a separate category from dysmenorrhea. Pelvic pain is not a symptom of PMS, unless other disorders are present, such as endometriosis. PMS may be confused with other disorders

TABLE 37. Conditions worsened by menstruation

Acute intermittent porphyria
Erythema multiforme
Migraine headaches
Periodic fever
Periodic hypersomnia
Periodic paralysis
Recurrent anaphylaxis
Rheumatoid arthritis

including hypothyroidism, chronic fatigue syndrome, collagen vascular disorder, anemia, diabetes mellitus, and others.[1,6,9] A number of conditions can be worsened by menstruation and can add to the differential diagnostic confusion (Table 37).

PMS Etiology. Although the precise etiology is not known, etiologic theories often center on dysfunction of serotonin or γ-aminobutyric acid A.[1,6,9] For example, one theory implicates heightened sensitivity to hydroxy-tryptamine receptors with reduced levels and impaired uptake of serotonin. Some research has concluded that anxiety can be enhanced by dysfunctional interaction of metabolites of progesterone and receptors of γ-aminobutyric acid A receptors. Other research notes that increasing late luteal phase levels of P_{CO2} can induce reduced threshold for a panic attack. Recurrent episodes of PMS may lead to increased sensitization to these mechanisms and more PMS symptomatology. Current research implicates a complex interaction between prostaglandins, central neurotransmitters (as serotonin), endogenous opioid peptides, peripheral autonomic nervous system, and ovarian steroids. Psychological issues may be worsened by PMS symptoms but are not primarily causative of PMS.

PMS Management. General measures often recommended for youth with PMS include adequate rest, exercise, regular hot baths, reduced intake of caffeine as well as sugar, reduced salt intake, avoidance of alcohol, and reduction in factors causing excessive stress.[1,6,9] If depression or anxiety is noted, psychological management may be helpful.[133] Beneficial effects on the emotional features of PMS have been seen by using selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine (20 mg daily), sertraline (50 mg daily), or paroxetine (20 mg daily).[1,6,9,128,134,135] The U.S. Food and Drug Administration has placed a "black box" warning on SSRIs due to increased suicidal ideation and behavior noted in children and adolescents taking SSRIs.[136] Patients with anxiety may benefit from the use of anxiolytics (alprazolam or buspirone). Tricyclic antidepressants have been helpful as well, including clomipramine.[136]

Although not recommended for adolescents, adult females with severe PMS have reported improvement with gonadotropin-releasing hormone (GnRH) agonists (such as leuprolide [Lupron] and buserelin [Suprefact]) that induce a medical oophorectomy by suppressing gonadotropin release with resultant suppression of ovulation and ovarian hormone synthesis. NSAIDs (such as ibuprofen) may be helpful probably by improving breast and/or pelvic pain. Diuretics (such as hydrochlorothiazide or spironolactone) may be beneficial in some by improving PMS edema or weight gain; however, abuse of diuretics may lead to increased edema. Bromocriptine is a dopamine-receptor agonist that has been used in adult females to relieve severe mastalgia seen in some with PMS. Measures attempted, but without specific research to verify benefit, include oral contraceptives, progesterone, thyroid hormone supplementation, lithium, evening primrose oil, atenolol, prostaglandin inhibitors, vitamin E or B_6 supplementation, and supplementation with calcium or magnesium.[1,6,9,137]

Pelvic Pain

Mittelschmerz. This refers to pain in the lower abdominal quadrants that occurs in the middle of the menstrual cycle in association with ovulation.[1,9,138] The cause of the pain is probably the result of pelvic irritation induced by contents of the discharged (dominant) ovarian follicle. Mittelschmerz (German: *middle pain*) does not occur in anovulation. The pain or discomfort is usually unilateral, crampy, and lateralized, lasts from several hours to 4 days, and typically changes sides from month to month. It may be accompanied by mild bleeding or vaginal secretion changes. Fortunately Mittelschmerz is rarely severe but sometimes can be confused with an ovarian cyst, ovarian torsion, ectopic pregnancy, or appendicitis. Management includes education of its cause, reassurance, analgesics, and, if severe, ovulation inhibition with oral contraceptives.

Endometriosis. Endometriosis involves the development of functional endometrial tissue (ie, stroma and glands) outside the uterus.[1,6,139-141] Although it mainly presents in adult females in the third and fourth decade of life, it may be seen in adolescent females as well; it has been reported as young as 10½ years of age. Incidence of 10%-17% has been reported in adult females and 40%-65% or more of adolescents with chronic pelvic pain (including secondary dysmenorrhea) may have endometriosis as noted on laparoscopy.[1,140-142]

Etiology. Endometrial tissue can be refluxed from the oviducts during menstruation in a condition termed *retrograde menstruation* or endometrial tissue may develop from many small cysts found on various structures: ovaries, surface of the uterus, pelvic ligaments, or the

peritoneum (*coelomic metaplasia*). Etiologic theories include genetic factors, lymphatic-vascular metastases, and immunologic deficiencies in which cell-mediated defects lead to endometrial cells that are not cleared from nonuterine structures.[1,139-143] Endometriosis can be found in 7% of close relatives of a patient with this condition, in contrast to 1% of controls.[1] The pain of endometriosis develops when endometrial cysts enlarge or swell during the menstrual cycle; pain can also occur because of pelvic adhesions or because nerve endings are stimulated.

Symptomatology. Classic features of endometriosis include severe dysmenorrhea, pelvic mass, and infertility.[140-143] Symptoms can be similar in adolescents versus adult females, although adolescents are more likely to have congenital reproductive tract anomalies (such as imperforate hymen, transverse vaginal septum, uterine anomalies, hematometra, hematocolpos) and renal agenesis.[144] The dysmenorrhea may be localized to the lower abdomen, groin, thigh, back, or deep in the pelvic. The pain can be worsened by coitus, improved with rest, and may become cyclical, acyclical, and chronic. There is no correlation between the intensity of the pain and the extent of endometriosis (ie, the number of endometriotic lesions does not correlate with the severity of the pain).

There may be abnormal menstrual bleeding (including bleeding before menses), dysuria, clinical hematuria, suprapubic pain, and dyspareunia. There may be primary amenorrhea with normal sexual development; in others there is dysfunctional uterine bleeding or persistent pain worsening with menstruation. Bowel symptomatology may occur especially in the late luteal and menstrual phases; these symptoms include rectal pressure, urgency, and pain with defecation (dyschezia). The symptoms can be modified by complications including adhesions, mass effects, internal bleeding, or even changes in bowel or bladder functions. Endometriosis can present as an adnexal mass, large ovarian endometriomas, or with diffuse disease.

Diagnosis. The correct diagnosis of endometriosis begins with a careful history as reviewed under Symptomatology above. The *pelvic examination* may be normal or, especially if performed during the late luteal phase of the menstrual cycle, may reveal pelvic tenderness, thick broad ligaments, immobile (fixed) uterus, or variable nodularity with or without tenderness (Table 38). *Ultrasonography* may reveal various cysts scattered in the pelvis or may reveal an adnexal mass, while a pelvic MRI is the best procedure to identify genital reproductive tract anomalies and a hysterosalpingography can be useful as well. CA-125 (cell-surface antigen) can be increased in patients with endometriosis and, although

TABLE 38. Differential diagnostic approach to pelvic pain*

Characteristics of Pain	Likely Diagnosis	Confirmatory Investigations
■ Midline location		
Cyclical, normal bleeding	Primary dysmenorrhea	History; pelvic examination (normal)
	Endometriosis	Pelvic examination; sonography; laparoscopy
Acute, irregular bleeding	Endometritis	Pelvic examination, cultures; CBC; sedimentation rate
	Threatened or septic abortion	History; pelvic examination; pregnancy test
Unrelated to menses, urinary symptoms[a]	Cystitis	History; urinalysis, urine culture
	Normal uterine pregnancy	History; pregnancy test
■ Lateral location		
Cyclical, normal bleeding	Mittelschmerz	History (timing, nature); pelvic examination (normal)
	Endometriosis	Pelvic examination; sonography; laparoscopy
Acute, postmenstrual	Salpingitis or pelvic inflammatory disease	History; pelvic examination, cultures; CBC, sed rate; laparoscopy
	Ectopic pregnancy	History; pelvic examination, pregnancy test
Acute, abnormal bleeding	Appendicitis	History; physical examination; CBC; radiography
	Ureteral colic	History; urinalysis; radiography
Unrelated to menses, acute	Constipation	History; rectal examination
	Pelvic osteomyelitis	Physical examination; radiography; gallium scan
Unrelated to menses, chronic	Psychogenic	History; exclusion of others; psychosocial evaluation

Abbreviation: CBC, complete blood count.

[a]Dysuria and urinary frequency may be associated with infection, pregnancy, and psychogenic factors.

*Reprinted, with permission, from Greydanus DE. Breast and Gynecological Disorders. In: Hofmann AD, Greydanus DE, eds. Adolescent Medicine, 3rd ed. Stamford, CT: Appleton & Lange, 1997:547.

it has a low sensitivity (ie, is not a good screening test), serum levels of CA-125 have been used to follow patient response to management.[1]

Laparoscopy with biopsy is the confirmatory test for endometriosis and is recommended for females with chronic pelvic pain of unknown cause that does not improve with NSAIDs and oral contraceptives.[1,6,140-146] Endometrial lesions in youth may have a different appearance than in

TABLE 39. Causes of chronic pelvic pain in women*

- Gynecologic
  - Noncyclical
    - Adhesions
    - Endometriosis
    - Salpingo-oophoritis
      - Acute
      - Subacute
    - Ovarian remnant syndrome
    - Pelvic congestion syndrome
    - Ovarian neoplasms
    - Pelvic relaxation
- Cyclic
  - Primary dysmenorrhea
  - Secondary dysmenorrhea
    - Imperforate hymen
    - Transverse vaginal septum
    - Cervical stenosis
    - Uterine anomalies (congenital malformation, bicornuate uterus, blind uterine horn)
    - Intrauterine synechiae (Asherman's syndrome)
    - Endometrial polyps
    - Uterine leiomyoma
    - Adenomyosis
    - Pelvic congestion syndrome
    - Endometriosis
- Cyclic
  - Atypical cyclical
    - Endometriosis
    - Adenomyosis
    - Ovarian remnant syndrome
    - Chronic functional cyst formation
- Gastrointestinal
  - Irritable bowel syndrome
  - Ulcerative colitis
  - Granulomatous colitis (Crohn's disease)
  - Carcinoma
  - Infectious diarrhea
  - Recurrent partial small bowel obstruction
  - Diverticulitis
  - Hernia
  - Abdominal angina
  - Recurrent appendiceal colic
- Genitourinary
  - Recurrent or relapsing cystourethritis
  - Urethral syndrome
  - Interstitial cystitis
  - Ureteral diverticuli or polyps
  - Carcinoma of the bladder
  - Ureteral obstruction
  - Pelvic kidney
- Neurologic
  - Nerve entrapment syndrome
  - Neuroma
- Musculoskeletal
  - Low back pain syndrome
  - Congenital anomalies
  - Scoliosis and kyphosis
  - Spondylolysis
  - Spinal injuries
  - Inflammation
  - Tumors
  - Osteoporosis
  - Degenerative changes
  - Coccydynia
  - Myofascial syndrome
- Systemic
  - Acute intermittent porphyria
  - Abdominal migraine
  - Systemic lupus erythematosus
  - Lymphoma
  - Neurofibromatosis

*Reprinted, with permission, from Rapkin AJ, Reading AE. Chronic pelvic pain. Curr Probl Obstet Gynecol Fertil 1991;14:101.

adult females and the examiner must be familiar with lesions found in adolescents.[140,143] Early lesions of endometriosis are pigmented, pale, cystic, vesicular, or hemorrhagic; more typical adult lesions reveal areas characterized with retraction, fibrosis, "powder burn" lesions, or overt endometriomas that can be very small or several centimeters in diameter.

Differential Diagnosis of Chronic Pelvic Pain. Tables 22 and 38-40 list causes of acute and chronic pelvic pain in adolescent and adult females.[147,148] Consultation is often necessary with experts in gynecology, surgery, urology, and others.[1,6,9,147,148] A thorough history and physical examination is important to identify the specific cause along with various laboratory testing that includes complete blood count, urinalysis (with urine culture), pregnancy testing, and STD testing (*C. trachomatis*, *N.*

TABLE 40. Differential diagnosis of pelvic masses*

Characteristic of Mass	Differential Diagnosis	Confirmatory History, Findings, and Procedure
■ Midline location		
With amenorrhea or abnormal menses	Pregnancy	History of sexual activity; positive pelvic examination
	Hematocolpos, hematometra	History of no menses, cyclic pelvic pain; perineal examination reveals imperforate hymen, vaginal stenosis
With normal menses	Uterine sarcoma (rare)	Negative pregnancy test; uterine enlargement; sonography CT; tissue diagnosis
	Bladder	History of acute retention; findings of herpetic or other lesions precipitating retention; catheterization
■ Lateral location		
With amenorrhea or abnormal menses	Functioning ovarian cyst	History of menstrual irregularity; negative pregnancy test; unilateral mass; physical or laboratory evidence of hormonal abnormalities; sonography, laparoscopy, tissue diagnosis
	Ovarian tumor	
	Polycystic ovary syndrome	As above with bilateral ovarian enlargement
With normal menses	Ectopic pregnancy	History of sexual activity; pregnancy test may or may not be positive; sonography; may or may not have pain or tenderness; may present as acute emergency
	Tuboovarian abscess	History and findings compatible with pelvic inflammatory disease; sonography, laparoscopy
	Nonfunctioning ovarian cyst	History of pain or asymptomatic; unilateral mass; may be very large; sonography, laparoscopy, tissue diagnosis
	Appendiceal abscess	History of appendicitis (or acute abdominal condition); positive rectal or abdominal examination; may be difficult to distinguish from pelvic inflammatory disease; sonography, laparotomy
	Fecal impaction	History of constipation; positive rectal or abdominal examination; abdominal roentgenograms

Abbreviation: CT, computed tomography.

*Reprinted, with permission, from Greydanus DE. Breast and gynecological disorders. In: Hofmann AD, Greydanus DE, eds. Adolescent Medicine, 3rd ed. Stamford, CT: Appleton & Lange, 1997:559.

TABLE 41. Treatment options for endometriosis

Oral contraceptives
Medroxyprogesterone acetate (Provera or Depo-Provera)
Androgens (methyltestosterone)
Gonadotropin-releasing hormone agonists (leuprolide acetate or nafarelin acetate)
Danazol (danocrine)
Anastrozole (Arimidex)
Laparoscopic ablation
LUNA (Laser Uterosacral Nerve Ablation)
Electrocautery
Thermocoagulation
Laparotomy with resection of endometriomas
Presacral neurectomy
Correction of associated congenital reproductive anomalies

gonorrhoeae, others).[126,149] Pelvic ultrasonography and diagnostic laparoscopy are often important aids in identifying a specific etiology. Laparoscopic results in patients with *acute* pelvic pain include a normal pelvis in 30%, ovarian cysts in 40%, pelvic inflammatory disease in 30%, appendicitis in 10%, adnexal torsion in 5%, and ectopic pregnancy in 3%.[150] Laparoscopic findings in patients with *chronic* pelvic pain of 3 months' duration or more include endometriosis in 45%, a normal pelvis in up to 40%, pelvic inflammatory disease in up to 15%, postoperative adhesions in up to 13%, uterine anomalies in 5%-8%, and ovarian cysts in 5%.[150]

Management. Table 41 and Fig 4 list treatment options for endometriosis, which is a chronic condition of variable severity that requires consultation with gynecologic consultants.[151]

NSAIDs are not usually helpful in relieving the pain of endometriosis. Reduction and even disappearance of endometrial tissue outside of the uterus may occur with the use of OCPs, transdermal or transvaginal hormonal contraceptives, or *medroxyprogesterone acetate* (Provera [30-50 mg orally once a day] or Depo-Provera [150 mg intramuscularly once a month or every 3 months]).[1,6,143] Side effects of progestins include weight gain, irregular bleeding, depression, bloating, and others. A progestin-dominant oral contraceptive may be helpful in some.

Another treatment option is *methyltestosterone* (5-10 mg bucally each day) since androgens inhibit endometrial growth. Side effects of androgens include virilization of the female and teratogenic potential (masculinization of a female fetus). Gonadotropin-releasing hormone agonists (leuprolide acetate or nafarelin acetate) are also used alone or in combination with estrogen because these agonists induce a state of menopause that is reversible, leading to absence of menses, vaginal

dryness, hot flashes, and bone loss. These agonists are typically withdrawn after 6 months, although adding estrogen may allow longer agonist use. *Danocrine* (Danazol) is a 17-α-ethinyl-testosterone derivative and is also used; it is prescribed at 400 mg twice a day orally, leading to improvement of pain in 90%.[143] Adverse effects include weight gain, edema, abnormal liver function tests, fetal androgenization, acne, lipid dysfunction, and others. Anastrozole is a drug (aromatase inhibitor) used to treat breast cancer that has been used in adult women with endometriosis along with oral contraceptives to treat endometriosis.[152]

Surgical management options are noted in Table 41.[1,6,140,141,143,145,150-155] Hormonal treatment can be provided after surgery because endometriosis often continues after surgical treatment. Correction of congenital anomalies that may be present is also important, as, for example, correction of an imperforate hymen, a transverse vaginal septum, or excision of a rudimentary blind horn. Surgery should seek to preserve fertility if possible.

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