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Adolescent female menstrual disorders

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Abstract

This paper reviews basic concepts of menstrual disorders in adolescents beginning with an overview of menstrual physiology followed by consideration of various abnormal menstrual patterns: amenorrhea (primary and secondary), dysfunctional uterine bleeding, dysmenorrhea (primary and secondary), and premenstrual syndrome.

Keywords: Adolescence, female, menstruation

Introduction

Menarche, or the onset of menstruation, occurs on average at 12.7 years of age in American females (approximately 12.16 years in African-American females versus 12.88 years in Caucasian females) (1). A responsive H-P-O (hypothalamic-pituitary-ovarian) axis induces cyclical menstruation that is regulated by levels of estrogen and progesterone and results in three classic menstrual phases: follicular, ovulatory, and luteal (4). Regulation of the onset and regularity of menses is under many influences, as listed in Table 1 (4). The level of exercise in adolescents involved in sports can have considerable influence on their menstrual patterns (5).

Adolescent menstrual patterns

The menstrual pattern of a mature female adult has a mean interval of 28 days (+/- 7 days) and a median blood loss of 30 ml per month, with 60-80 mL per month often set as upper limits of normal blood loss (6). There is more variability in the adolescent female, often due to lack of regular ovulation for several months to several years after menarche. Approximately half of her cycles are anovulatory in the first two years after menarche and 20% are still without ovulation by the fifth menstrual year.

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Table 1. Influences on the Menstrual Cycle

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

The median cycle length for adolescent females is 31 days in the first two years after menarche, in contrast to 28 days for the adult female. Approximately 38% of cycles at 2 years after menarche are less than 40 days. This classic lack of ovulation in the adolescent female may result in oligomenorrhea, amenorrhea or dysfunctional uterine bleeding. Definitions of menstrual abnormalities are noted in Table 2. Menstrual disorders discussed below include amenorrhea, dysfunctional uterine bleeding, and dysmenorrhea.

Table 2. 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

** Reprinted, with permission, from: Greydanus DE: Breast and Gynecological Disorders. In: Adolescent Medicine, 3rd Edition. Eds: AD Hofmann and DE Greydanus. Stamford, CT: Appleton and Lange, ch. 25: page 547, 1997.

Amenorrhea

The absence of menses is called amenorrhea, and is defined as primary or secondary amenorrhea (7-9). The definition of primary amenorrhea is the absence of menstruation by 14 years of age with a sexually maturity rating (SMR) of 1 or by 16 years of age at a SMR of 2 or greater. Once menses has started, the lack of periods for three cycles or for 6 months defines secondary amenorrhea. Oligomenorrhea refers to infrequent, irregular menstrual bleeding with greater than 45 day cycles. Although amenorrhea can be normal in the adolescent for three to six months during the first two years after menarche, a number of medical conditions can be the cause for an adolescent presenting with amenorrhea (primary or secondary) or oligomenorrhea (see Tables 3 and 4). Tables 3, 5, 6 list various laboratory tests useful in this clinical evaluation. The most common cause of secondary amenorrhea is pregnancy. Once pregnancy has been ruled out, laboratory testing will eliminate or confirm hyothyroidism and hyperprolactinemia as potential diagnoses. It is important to consider the remaining causes of secondary amenorrhea classified as normogonadotropic amenorrhea, hypogonadotropic hypogonadism, and hypergonadotropic hypogonadism, each having specific etiology. The most common causes of normogonadotropic amenorrhea . are outflow obstruction and hyperandrogenic chronic anovulation. Polycystic ovarian syndrome (PCOS) is the most common cause of hyperandrogenic chronic anovulation. The high prevalence of secondary amenorrhea seen in adolescent athletes warrants further discussion.

Table 3. Gynecological disorders of adolescent females

Gynecologic disorder	Special comments	Differential diagnosis	Laboratory testing
Amenorrhea (Primary)	Physiologic is the main cause; MRKH syndrome assoc. with Renal abnormalities and Spinal malformations. Short stature with delayed sexual maturation: Turner syndrome; delayed sexual maturation + hypertension seen in 17-α-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 gonodotropins (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) Dysmenorrhea (Secondary)	Pelvic pain during normal ovulatory menstruation; no underlying pelvic pathology. May also see gastrointestinal symptoms, headache, myalgia, sweating. May be seen at menarche or 3+ years post-menarche.	Physiologic 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
Endometriosis	Presentation in adolescence not the same as in adults. May have acyclic pain, abnormal uterine bleeding, GI symptomatology	See secondary dysmenorrheal	Laparoscopy Laparotomy

Table 3. (Continued)

Gynecologic disorder	Special comments	Differential diagnosis	Laboratory testing
Mittelschmertz	Pain associated with ovulation in the middle of a menstrual cycle. May last 1-3 days and be mild to severe.	See secondary 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, muco-purulent 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.	**Non-specific:** 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 (11ß-hydroxylase, 21-hydroxylase, 3ß-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-α-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; F; Fahrenheit; C: Centigrade; 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, Feinberg AR, Patel DR, Homnick DN, eds. The Pediatric Diagnostic Examination. New York: McGraw-Hill, 2008.

Table 4. 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)
- E. 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. Pediatric Clin No Amer 49:553-580, 2002.

Table 5. Methods to Evaluate Hypoestrogenemia in Adolescents

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

Amenorrhea in adolescent athletes

Amenorrhea and oligomenorrhea are commonly encountered in the adolescent athlete population (10,11). Menarche may be delayed in an adolescent athlete five months for each year of intense, pre-pubertal exercise. Furthermore, secondary amenorrhea is well-described in female athletes participating in cycling, gymnastics, and running sports. Menstrual dysfunction is noted in 12% of swimmers as well as cyclists, 44% of ballet dancers, 50% of female triathletes, 51% of endurance runners, and up to 20% of strenuously exercising females in general (12). Research suggests that up to 15% of all female athletes and two-thirds of elite female athletes have menstrual dysfunction. As noted by Table 1, there are many factors influencing menstruation in adolescent athletes. Tables 3 and 4 note the etiology of amenorrhea. The most common cause of amenorrhea in athletes involved with intense exercise is hypogonadotropic hypogonadism in which there is dysfunction of the GnRH production and LH pulsativity. Low body fat, although is a factor, is not the sole reason for menstrual dysfunction. The role of leptin in the complex menstrual process is not yet clear. Previous theories implying that menstruation cannot occur below a body fat percentage of 17% are not proven (12). Low body weight by itself does not cause amenorrhea and the weight of a female athlete with no menses can be the same or even more than one with a normal menstrual pattern.

Table 6. Laboratory Testing for Amenorrhea in Adolescents

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

The intense exercise pattern induces such a major energy drain that the caloric intake of this athlete is not sufficient to maintain normal menstrual function. Meeting the energy needs of the athlete is the cornerstone to restoring normal menstrual function. This treatment is further discussed.

Management of amenorrhea

The management of an adolescent female with amenorrhea or oligomenorrhea is determined by the underlying cause(s) of the menstrual dysfunction. If an intense exercise pattern is a central theme, the clinician can recommend a reduction in exercise by 10% or more. Typically in the female athlete triad (i.e., irregular menses as amenorrhea, disordered eating, and osteopenia—osteoporosis) (4), eating patterns may be abnormal as well, and she should be advised to improve her nutritional intake, including calcium and vitamin D supplementation. Consultation with a sports nutritionist can help the patient ensure she is meeting the nutritional and caloric needs specifically during involvement in sports. If menstrual dysfunction is part of a chronic hypoestrogenemia (see Table 5), she is at increased risk for reduced bone mineral density, osteopenia and eventually osteoporosis. Females with chronic lack of menstruation and low bone mineral density (BMD) may never acquire a normal BMD even if the menstrual pattern eventually is normalized.

Female athletes with low BMD are at increased risk for the development of stress fractures. Daily supplementation with calcium (1000-1500 mg per day), Vitamin D (400-800 IU per day), Vitamin B Complex, and Vitamin E (100-200 IU per day) is recommended for this athlete with menstrual dysfunction and/or eating dysfunction (10). Approximately 50% of bone mass is acquired during the adolescent years, and thus, if the female adolescent athlete has a low BMD, estrogen supplementation (conjugated estrogen or oral contraceptives) is suggested by many clinicians in an attempt to help her prevent bone loss.

The American Academy of Pediatrics has recommended that the amenorrheic adolescent athlete not be given hormonal medication if she is within three years of menarche; instead, she should be advised to lower her exercise pattern intensity and correct her nutritional intake (including adequate calcium intake) (13). Estrogen supplementation (typically the oral contraceptive) is recommended for the amenorrheic athlete if she is over 3 years from menarche and over age 16; hormonal management can used for those under age 16 years, if there is a history of a stress fracture.

However, problems in the management of these athletes often arise. For example, many committed athletes will not lower their intense exercise patterns nor alter their unhealthy dietary habits. Also, estrogen supplementation is controversial and not proven to enhance or protect BMD, with or without weight gain. It is not currently proven what the actual acute or chronic implications are of chronic amenorrhea and potential estrogen deficiency in the female adolescent athlete or in other females with these issues.

The use of conjugated estrogen or the oral contraceptive does not correct the underlying menstrual dysfunction and after the estrogen is stopped, the abnormal menstrual pattern often

resumes. There are also a number of potential side-effects to oral contraceptives, including breast tenderness, breast congestion, nausea, emesis, weight gain, and others.

Some studies suggest that oral contraceptives under 50 mcg estrogen may not be helpful in preventing osteoporosis (4). BMD is usually the most reduced in those who are thin and not active. Intense exercise involving weight bearing leads to high mechanical forces neutralizing the low BMD effect of a thin body type; bone accretion may be enhanced by weight-bearing exercise, allowing some amenorrheic athletes (i.e., tennis players, ice skaters, runners, gymnasts) to have normal or increased BMD.

Management of polycystic ovarian syndrome

Polycystic ovarian syndrome (PCOS) is characterized by hyperandrogenism and chronic oligo-ovulation (14). The clinical presentation is heterogenous and often difficult to recognize in adolescents due to the coinciding signs and symptoms of puberty including increased androgen production. Table 3 provides key features of PCOS as well as a differential diagnosis and suggested laboratory evaluation. Table 7 lists laboratory results which may be found in PCOS and support the diagnosis. Table 8 lists potential management options for adolescent females with PCOS. Treatment of PCOS is multifactorial and includes addressing obesity if present, decreasing androgen levels, and improving insulin resistance. Oral contraceptives (OCP's) are the mainstay of treatment in PCOS. OCP's decrease LH secretion and thus decrease ovarian androgen secretion, protect the endometrium from unopposed estrogen stimulation, and increase sex hormone binding globulin which then decreases free testosterone to improve hirsutism and acne. No specific OCP has shown to be more effective; however, Yasmin which contains both ethinyl estradiol and drosperinone decreases both ovarian and adrenal androgen secretion. Medroxyprogesterone (Provera—10 mg) or micronized progesterone (Prometrium) can also be prescribed to induce withdrawal bleeding if this is taken orally for 12-14 days each month.

Table 7. Laboratory Test Results in PCOS Patients

Hyperinsulinemia (fasting levels of glucose/insulin ratio <4.5)
LH : Mild ↑
FSH: Low limits of normal
LH-FSH ratio: > 2.5:1
Estrodiol: Moderate ↑
17-hydroxyprogesterone: mild ↑
Androgen: mild to moderate ↑ in levels
- -free and total testosterone
- -early morning urinary 17-ketosteroids
- -androstenedione
- -dehydroepiandrosterone sulfate (DHEAS) (can also be normal)

Sex hormone-binding globulin (SHBG): ↓
Prolactin: Mild ↑
Abnormal lipid profile
- -↓ high-density lipoprotein
- -↑ cholesterol
- - ↑ very-low density lipoprotein
- - ↑ low-density lipoprotein
- - ↑ triglycerides

Table 8. Management Options for PCOS Patients

Combined oral contraceptives
Transdermal (patch) contraception
Transvaginal hormonal contraceptives (Nuva Ring)
Progesterone
Spironolactone (androgen receptor antagonist) (hirsutism)
Flutamide (androgen receptor antagonist) (hirsutism)
Metformin
Management of obesity
Management of acne vulgaris
Hair removal (Electrolysis and Thermolysis)
Ovulation induction (usually only for adults)
- Clomiphene citrate
- GnRH agonistic analogs (leuprolide acetate or nafarelin)
Laser "drilling" of the ovary (↓ ovarian stromal steroids by reducing the stroma)
Management of potential co-morbid endocrinopathies

The treatment of hirsutism can include shaving, bleaching, depilatories and electrolysis. Pharmacologic treatment includes eflornithine (Vaniqua) which is an approved topical cream that acts as a hair growth retardant.

Androgen receptor antagonists (such as spironolactone [50 to 100 mg twice a day]) or antiandrogens (such as flutamide or cyproterone acetate), though not approved for the treatment of hirsutism, are commonly used. Metformin (Glucophage) can be used to lower serum insulin levels along with reducing ovarian cytochrome P450c17a activity and improving hyperandrogenism found in obese PCOS adolescent females.

Early intervention with androgen suppression therapy along with exercise and proper nutrition can improve the lives of these youth in their future adulthood. It is also important to address comorbid conditions including depression and other mental health concerns. Future complications of adolescents with PCOS include the potential of endometrial carcinoma, diabetes mellitus (type 2), infertility, cardiovascular disease, and hyperlipidemia.

Dysfunctional uterine bleeding

Excessive, sustained, or unpatterned uterine bleeding not caused by anatomical lesions defines dysfunctional uterine bleeding (DUB). It is one of the most common menstrual concerns of adolescent females and is noted in about 15% of all females seeking gynecologic consultation. DUB may lead to anemia (ranging from mild to severe), absence from school (or work), spontaneous muscle or joint bleeding, or post-surgical bleeding.

Tables 3 and 9 provide a list of DUB etiologies that include anovulation, complications of pregnancy, anomalies of the reproductive tract, disorders of coagulation, trauma, endocrinopathies, other systemic disorders, infection (such as pelvic inflammatory disease or PID), and others (4). Table 3 provides suggested laboratory tests that may be obtained in the evaluation of DUB.

DUB management

Treatment of dysfunctional uterine bleeding consists of treating the symptoms associated, as well as the cause.

The first step, next to identifying the cause, is diagnosing the level of anemia, which is based on the classification of mild anemia (hematocrit over 33% or hemoglobin over 11 g/dl), moderate anemia (hematocrit 27 to 33% or hemoglobin 9 to 11 g/dl), or severe anemia (hematocrit under 27% or hemoglobin under 9 g/dl and/or dropping) (15,16).

Table 9. Causes of Abnormal Vaginal Bleeding*

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 (von Willebrand's disease; Glanzmann's disease)
Clotting disorders (hemophilia; 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)
Continual estrogens
Other drugs
Danazol

Table 9. (Continued)

				Spironolactone
				Anticoagulants
				Platelet inhibitors
				Chemotherapy drugs
				Natural hormones from plant extracts (DHEA, Dong Quai, Yam Extract)
		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.

*Reprinted, with permission, from: Greydanus DE: Breast and Gynecological Disorders. In: Adolescent Medicine, 3rd Edition. Eds: AD Hofmann and DE Greydanus. Stamford, CT: Appleton and Lang.

Absence of anemia or mild anemia

Reassurance and monitoring over time is often all that is needed for mild DUB with no or mild anemia. The patient can be instructed to carefully follow her menstrual cycles with a menstrual calendar that can be presented at office visits for review by her clinician. If mild anemia is present evaluate dietary inatke and supplement with 300 mg of ferrous sulfate three times a day. Table 10 outlines potential adverse effects from iron supplementation. A slow release formulation can decrease some side effects. Constipation is a common side effect and therefore, a stool softener is often started when iron is supplemented. Vitamin C is often also added to each dose of ferrous sulfate to enhance absorption.

Table 10. Adverse Effects of Iron Supplementation

Nausea
Emesis
Constipation (add stool softener to prevent)
Diarrhea
Stools that are black
Discoloration of urine
Worsening ulcers/colitis

In addition to treating the anemia, combined oral contraceptives (also, patch or nuvaring) can be used to help regulate menses and help avoid unwanted pregnancy. Depo-medroxy-progesterone acetate (DMPA) is not typically recommended as it may worsen the menstrual irregularity and potentially lead to amenorrhea; an intramuscular injection should be avoided in those with coagulation disorders. NSAIDs (non-steroidal anti-inflammatory drugs) are helpful in reducing menstrual blood flow by as much as 50% via a direct effect on the endometrium that balances the vasodilator prostaglandin I2 and the potent vasoconstrictor thromboxane A2 (17-19).

Moderate anemia

Combined oral contraceptives (typically a 30 to 35 mcg ethinyl estrodiol type) are used to control bleeding in patients with DUB marked by moderate anemia. The importance of estrogen is that it binds to receptors in the endometrium, provides stabilization of the endometrial vasculature and stroma, and stimulates specific growth factors.

The pill can be provided 2 to 4 times a day until the bleeding has stopped and then gradually tapered over 14 to 21 days to allow for withdrawal bleeding. It can be continued at a once a day dosage for the next few months or longer if necessary. A longer dosing pattern (3-6 months) will also allow correction of the underlying anemia.

Higher levels of estrogen may cause nausea and therefore, an anti-emetic medication can be added to alleviate any nausea or emesis that may occur. Iron supplementation can be provided as discussed previously.

An alternative to use of an oral contraceptive is prescription of oral equine estrogen (2.5 mg for 21-25 days each month) followed by medroxyprogestone acetate (10 mg a day) for the last 7 days of the menstrual cycle. The use of progesterone-only agents is preferred by some clinicians, as outlined in Table 11. Initially, high doses may be needed to induce endometrial atrophy and then estrogen can be continued for a number of days to avoid break-through bleeding.

Some physicians add an oral progesterone agent over the last 10 days of the menstrual cycle each month to avoid unopposed estrogen effects, allow endometrial stabilization and allow organized endometrial sloughing. Concerns about using cyclic oral progestin therapy include potential bloating, acne vulgaris, increased appetite-induced weight gain, and reduced contraceptive effect.

Table 11. 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 day)
2. high dose may be necessary: 40-80 mg per day or 100 mg Depo IM/day
B. Norethindrone acetate
1. 10 mg q 4 hours, then q6-8 hrs to 12 hours; taper as bleeding decreases
2. May stay on 5 mg q 12 hrs for months if necessary with ↑ 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)

*Modified with permission from: Greydanus DE, Omar HA, Tsitsika AK, Patel DR: Menstrual disorders in adolescent females: Current concepts. Dis-A-Month 2009; 55(2): page 60.

Severe anemia

Intravenous fluids and blood products may be necessary in this situation along with high dose estrogen, such as use of intravenous conjugated equine estrogens (25 mg initially and repeat dose every 4-6 hours for up to 4 doses) (4,17-19).

The high dose estrogen induces rapid hemostasis because of increased production of fibrinogen, increased activity of Factors V and IX, and increased aggregation of platelets. Use of such high dose estrogen may increase thromoembolism risks.

An anti-emetic, again, is added to control the potential nausea and emesis. A progesterone agent is

added to induce controlled withdrawal bleeding from the endometrium. Some clinicians prefer to use an oral contraceptive dosing pattern (see Table 12) to avoid use of intravenous estrogen.

Table 12. Oral Contraceptive Schedule to Control Severe DUB*

1.	Utilize a monophasic combination OC with at least 35 mcg ethinyl estradiol
2.	Four times a day (with an anti-emetic) until the bleeding stops
3.	Three times a day for 4 days
4.	Twice a day for two to three weeks
5.	Allow a controlled withdrawal bleed
6.	Start the oral contraceptive and oral iron supplements at once a day for 3 to 6 months

*Modified with permission from: Greydanus DE, Omar HA, Tsitsika AK, Patel DR: Menstrual disorders in adolescent females: Current concepts. Dis-A-Month 2009; 55(2): page 60.

Table 13. Effects and Benefits of Levonorgestrel IUD*

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

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 one year
- •Good for those with Mental retardation/Developmental Disorders
- •Frequent amenorrhea
- •Decreased dysmenorrhea
- •Decreased premenstrual syndrome
- •Very low rates of infectious complications

*Modified with permission from: Greydanus DE, Omar HA, Tsitsika AK, Patel DR: Menstrual disorders in adolescent females: Current concepts. Dis-A-Month 2009; 55(2): page 64.

Management of DUB due to coagulation disorders

Control of DUB in adolescent females with coagulation disorders can be complex and consultation with experts in hematology is recommended (4). The cornerstone of bleeding control is appropriate factor replacement therapy with additional pharmacologic agents that include intranasal DDAVP (1-deamino-8-D-arginine vasopressin) (Desmopressin acetate), antifibrinolytics (epsilonamino caproic acid [Amicar] or tranexamic acid (Cyklokapron), combined oral contraceptives, and/or levonorgestrel-releasing IUD (Mirena).

Combined oral contraceptives raise Factor VIII activity (FVIII:Ac) in hemophilia carriers. In patients with von Willebrand's disease, estrogen raises Factor VIII/vWF-ristocetin cofactor activity, and partially corrects prolonged bleeding time. If there is a history of deep vein thrombosis, and estrogen is used to control severe DUB, coumadin should be added as adjunctive therapy.

Other DUB anagement options

There are other treatment options commonly used in adults, but less commonly in adolescents with severe and/or persistent DUB. These potential management strategies include danocrine, GnRH agonists, and surgical options, such as dilation and curettage, and hysterectomy. Danazol (Danocrine) is a synthetic hormonal agent prescribed to manage endometriosis, breast cysts, and severe DUB in adult females. Its benefits includes estrogen suppression and cessation of menstruation (4). GnRh agonists (i.e. buserelin , leuprolide [Lupron Depo], and nafarelin [Synarel]) stop menstruation, but there is limited research data on their use in adolescent females.

Dysmenorrhea

Dysmenorrhea is typically divided into primary and secondary dysmenorrhea. Primary dysmenorrhea refers to menstrual pain with no underlying pelvic pathology; secondary dysmenorrhea refers to pelvic (menstrual) pain resulting from anatomic and/or pelvic pathology. Table 3 outlines the definition and differential diagnosis for dysmenorrhea.

Primary dysmenorrhea is often classified as mild, moderate, or severe. Mild dysmenorrhea does not interfere with normal daily activities and only minimal analgesic support is needed. With moderate dysmenorrhea, there is some reduction in activities and the use of analgesics is necessary.

Severe dysmenorrhea implies that regular activities do not occur during the active phase of the symptoms and analgesics are usually not beneficial. Approximately two-thirds of ovulating females report some menstrual discomfort for one to three days of most ovulatory cycles with about half having mild dysmenorrhea, one-third with moderate cramping, and about 14% with severe dysmenorrhea (4).

Primary dysmenorrhea is the most common medical reason for school or work absence and it has an increasing incidence from the early adolescent years to young adulthood and first pregnancy (20,21). Primary dysmenorrhea often starts 6 to 12 months post-menarche, though it may not been seen until the third year post-menarche.

The pain associated with menstruation may start before the initiation of menstrual flow or once menstrual flow starts. The symptoms associated with dysmenorrhea can vary patient to patient and are illustrated in Table 14. When a patient presents with dysmenorrhea, the first step is to differentiate primary from secondary dysmenorrhea (see Table 3). It is also helpful to identify factors which can alleviate or aggravate the pain (Table 15).

Etiology

The etiology of the menstrual cramping in primary dysmenorrhea is due to the conditions set after ovulation occurs with the increase and decrease in progesterone levels that induce release of prostaglandins that stimulate a rise in uterine contractions and endometrial nerve endings' irritation (21,23). The result is variable menstrual cramping and pain due to a rise in myometrial resting tone, increased frequency and amplitude of contractions, and a rise in dysrhythmic contractions.

Those with primary dysmenorrhea have higher levels of circulating prostaglandins during menstruation in contrast to those without such cramping. In addition, research suggests that those with primary dysmenorrhea have heightened sensitivity to prostaglandins in the circulation and also higher vasopressin levels that can lead to increased uterine contractions and increased menstrual pain.

Table 14. Features Associated with Primary Dysmenorrhea

Nausea
Emesis
General malaise
Fatigue
Muscle cramps
Backache
Low abdominal pain
Headache
Inner thigh pain
Diarrhea
Lightheadness (dizziness; flushing)
Dizziness

Table 15. Factors that Improve or Worsen Primary Dysmenorrhea

IMPROVE
Parity
Regular exercise
Oral contraception
NSAIDS
(non-steroidal anti-inflammatory drugs)
Progesterone IUD
WORSEN
Depression
Anxiety
Obesity
Longer menstrual flow
Copper IUD

Primary dysmenorrhea management

NSAIDs

The initial pharmacologic management for those with primary dysmenorrhea is non-steroidal anti-inflammatory drugs (NSAIDs) that includes non-selective (COX-1 and COX-2 inhibitors) (Table 16) and selective or COX-2 inhibitors. Efficacy in the management of primary dysmenorrhea includes the suppression of cyclic endoperoxide synthetase at the cyclooxygenase level. In general, there is often no difference in efficacy and choice of therapeutic agents is determined by cost, convenience, adverse effects, and patient preference. It is thought that enolic acids (i.e., oxicams) may not only be not as effective for primary dysmenorrhea, but also have many more side effects.

The NSAIDs with the highest benefit with lowest adverse effects are the propionic acids: ibuprofen, naproxen, naproxen sodium, and ketoprofen (Tables 16 and 17). Propionic acids are FDA approved for the treatment of primary dysmenorrhea and dosages are listed in table 17. Side effects include headache, gastrointestinal upset, heartburn, indigestion, rash, and dizziness. Naproxen sodium has a long half-life allowing for twice-a-day dosing. Ketoprofen has anti-bradykinin action, provides stabilization of lysosomal membranes, and inhibits prostaglandin as well as leukotriene synthesis.

Several propionic acids are available as over-the-counter agents and higher doses are available with prescription. As discussed previously, it is helpful for the patient to keep a calendar of her menstrual cycles so that she knows when her menses should start and can initiate pharmacologic therapy. Medication can be continued for two to four days as needed for pain and reduction of blood loss. Partial to near complete pain improvement is noted in about 80% of those with primary dysmenorrhea. Failure of benefit may be due to absence of prostaglandin synthetase inhibitors blocking the 5-lipooxygenase pathway that allows continued production of leukotrienes. It is also important to remember that if there is no improvement in pain, secondary dysmenorrhea should be considered.

Table 16. NSAIDs: Non-Selective (COX-1 and COX-2 Inhibitors)

1.	Salicylic acid esters: aspirin
2.	Acetic acids: indomethacin, sulindac, tolmetin, nabumetone
3.	Propionic acids: ibuprofen, naproxen, naproxen sodium, ketoprofen, flurbiprofen
4.	Fenamic acids:mefenamic acid, meclofenamate
5.	Enolic acids: piroxicam

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Salicylic acid esters (i.e., aspirin) are not efficacious in treatment of dysmenorrhea as it has limited anti-inflammatory effects on the endometrium. Indomethacin is an effective agent but has significant potential side effects including renal insufficiency, prolonged vaginal bleeding, headaches, gastrointestinal ulcers and gastric bleeding. Fenamic acids (mefenamic acid [Table 17], meclofenamate) have a rapid onset of action and can reduce bleeding in patients with menorrhagia. These medications act by blocking myometrial receptor sites for synthesized prostaglandins as well as lead to inhibition of 5-lipooxygenase activity (with resultant leukotriene production suppression).

Table 17. 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	25-50	25-50 mg q6-8h	300
Naproxen[a] sodium	550	275mg q6-8h or 550mg q12h	1375
Naproxen	500	***250mg q6-8h or 500mg q12h***	1250
Mefenamic acid	500	***250 mg q4h***	Not established

[a]Available as over-the-counter drugs in U.S.: ibuprofen; 200-mg tablets; naproxen sodium: 220-mg tablets.

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Table 18. Management Options for Primary Dysmenorrhea

NSAIDs (Tables 16 and 17)
Hormonal Contraception (Pill, patch, transvaginal, injectable, implantable)
Use a menstrual calendar (to identify menstrual pattern)
Ensure adequate rest, sleep, and exercise
Reduction of psychological factors (as depression, anxiety, excess stress)
Fish consumption (omega-6-fatty acids)?
Reduction of caffeine and sugar
Unproven methods
- Calcium channel blockers (i.e., nifedipine—tried in adult patients; can lead to headaches, hypotension)
- Acupuncture
- Transcutaneous electrical nerve stimulation (TENS).

Oral contraceptives

Combined oral contraceptives (COCs) may be used for primary dysmenorrhea if NSAIDS are not beneficial, as adjunctive management to NSAIDs, and also as first line therapy if the patient is seeking contraception. COCs prevent ovulation and block the development of the post-ovulatory rise in prostaglandin levels because of the ovulation-induced corpus luteum. Blood flow is often reduced and menstrual cramps are lessened in up to 95% of females with primary dysmenorrhea on COCs. Other forms of hormonal contraception are also efficacious, such as the patch, transvaginal, injectable, or implantable (subdermal) methods. If a combination of NSAIDs and hormonal contraceptives are not helpful to a considerable extent, consider that the patient may have secondary versus primary dysmenorrhea (see Table 3). Other management options for treatment of primary dysmenorrhea are listed in Table 18.

Secondary dysmenorrhea

There are many diagnoses in the differential for secondary dysmenorrhea including endometriosis, pelvic inflammatory disease, reproductive tract anomalies (Mullerian defects), and others (see Table 3). A careful medical history can often provide clues that an organic lesion is the cause of the dysmenorrhea. For example, the pain may begin at menarche or three years (or more) after the onset of

menses. There may be atypical pain, pain associated with DUB or changing menstrual patterns, pain that is not relieved with NSAIDS and hormonal contraception, and pain that develops after pelvic surgery.

Table 19. Medical History in a Patient with Dysmenorrhea*

Age at menarche
Last time menstruation were 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
Sexual history and use of any contraception
History of pregnancy (and its outcome)
History of sexually transmitted infections
History of dyspareunia
History of other systemic disorders (i.e., gastrointestinal, genitourinary, others)
History of surgical procedures
Family history of various gynecologic conditions (dysmenorrhea, endometriosis, ovarian cysts, infertility, virilization, cancer, others)

*Used with permission from: Greydanus De, Omar HA, Tsitsika AK, Patel DR: "Menstrual disorders in adolescent females" In: Pediatric and Adolescent Sexuality and Gynecology: Principles for the Primary Care Clinician. NY: Nova Science Publishers, Inc. ch. 7: 384, 2010.

Table 19 outlines questions to ask in the medical history to help delineate between primary and secondary dysmenorrhea. A careful examination and selective laboratory testing are necessary to identify the underlying cause (Table 3). Management is dependent on the underlying etiology (4). Endometriosis is one of the most common causes of secondary dysmenorrhea.

Endometriosis

The development of endometrial stroma and glands outside of the uterus defines the core feature of endometriosis. Though more commonly associated with adult females, it may been seen in half or more of adolescent females with chronic pelvic pain. Reflux of endometrial tissue from oviducts during menses may occur in a process termed retrograde menstruation; other mechanisms include the development of endometrial tissue from small cysts found over the pelvis, such as uterine surface, ovaries, pelvic ligaments, or the peritoneum (coelomic metaplasia).

The precise underlying mechanisms are unclear, and thus various theories are proposed to explain why endometrial tissues are not cleared from non-uterine locations; these theories include immunologic deficiencies, lymphatic-vascular metastases, and genetic factors. Recent research focuses on the major role of prostaglandin E2 (24). Pain arises in endometriosis because of swelling of endometrial cysts during menses, pelvic adhesion-induced pain, or stimulation of various pelvic nerve endings.

Symptomatology

Features consistent with endometriosis include severe dysmenorrhea unresponsive to analgesics or hormonal medication, chronic pelvic pain, and infertility. A variety of pain patterns exist depending on the location of the endometriotic lesions. There is no association between the number of lesions and the pain intensity. Abnormal menstrual bleeding can be seen along with various other symptoms, including clinical hematuria, suprapubic pain, dyspareunia, and/or dysuria. Variable gastrointestinal symptomatology may also be present and include pain with defecation (dyschezia), rectal pressure, and urgency. Endometriosis can also present with large ovarian endometriomas and adnexal masses.

Table 20. Differential Diagnostic Approach to Pelvic Pain*

Characteristics of Pain	Likely Diagnosis	Confirmatory Investigations
• MIDLINE LOCATION Cyclical,normal bleeding	Physiological 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[3]	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	History; pelvic examination, cultures;
Acute, abnormal bleeding	inflammatory disease	CBC, sed rate; laparoscopy
	Ectopic pregnancy	History; pelvic examination, pregnancy test
Unrelated to menses, acute	Appendicitis	History; physical examination; CBC; radiography
	Ureteral colic	History; urinalysis; radiography
Unrelated to menses, chronic	Constipation	History; rectal examination
	Pelvic osteomyelitis	Physical examination; radiography; gallium scan
	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.

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Diagnosis

Identifying the pattern and location of pain can help in differentiating the etiology. Table 20 outlines a diagnostic approach to adolescent females with pelvic pain. Table 21 outlines a diagnostic plan for pelvic masses. A pelvic examination in a patient with endometriosis may be normal or reveal various abnormalities, such as pelvic tenderness, fixed (immobile) uterine, thickened broad ligaments, and/or unpredictable nodularity with or without tenderness. Various pelvic cysts or an adnexal mass may be noted by ultrasonography while a pelvic MRI may reveal genital reproductive tract anomalies. Females with endometriosis may have an increased CA-125 (cell surface antigen). Although this test has a low sensitivity and is not a cost-efficient screening test, levels of this antigen can be used to follow clinical response to treatment. The gold standard of diagnosing endometriosis is laparoscopy with biopsy and this should be performed in adolescent females with chronic pelvic pain of unknown cause not responding to NSAIDs and hormonal medication. Endometriotic lesions can appear differently in adolescent versus adult females (4)

Table 21. 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
	Uterine sarcoma (rare)	Negative pregnancy test; uterine enlargement; sonography CT; tissue diagnosis
With normal menses	Bladder	History of acute retention; findings of herpetic or other lesions precipitating retention; catheterization
• LATERAL LOCATION		
With amenorrhea or abnormal menses	Functioning ovarian cyst (Table 3)	History of menstrual irregularity; negative pregnancy test; unilateral mass; physical or laboratory evidence of hormonal abnormalities; sonography, laparoscopy, tissue diagnosis
	Ovarian tumor	As above with bilateral ovarian enlargement
	Polycystic ovary syndrome (Table 3)	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
	Ectopic pregnancy (Table 3)	
With normal menses	Tuboovarian abscess (Table 3)	History and findings compatible with pelvic inflammatory disease; sonography, laparoscopy
	Nonfunctioning ovarian cyst (Table 3)	History of pain or asymptomatic; unilateral mass; may be very large; sonography, laparoscopy, tissue diagnosis
	Appendiceal abscess	History of appendicitis (or acute abnormal 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.

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Danazol, a steroidal androgen can be used which suppresses cyclic changes and eventually causes atrophy of the endometriotic sites. Careful observation of potential adverse effects is important and these may include including fetal androgenisation, thrombotic events, elevated liver function tests, hyperlipidemia, acne vulgaris, weight gain, edema, and others.

Management of endometriosis

Endometriosis is a complex and perplexing condition that should be managed in consultation with a gynecologist. There are many treatment options and these are listed in Table 22. NSAIDs (Table 17) are usually not beneficial in females with endometriosis while hormonal medications may be useful in

reducing (even removing) non-uterine endometriotic tissue. Clinicians can use oral contraceptives, patch contraception, transvaginal hormonal contraceptives, depo-medroxy-progesterone acetate (DMPA: 150 mg intramuscularly every three months), or oral medroxy-progesterone acetate (30-50 mg once a day). Adverse effects of progestins include irregular bleeding, bloating, weight gain, and others. If combined oral contraceptives are contraindicated, one may use a progestin-dominant oral contraceptive.

Table 22. 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

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Gonadotropin-releasing hormone agonists (leuprolide acetate or nafarelin acetate) can also be prescribed by themselves or in combined with estrogen. The addition of estrogen can help prevent the reversible state of menopause with amenorrhea, hot flashes, vaginal dryness, and loss of bone mass. If these agonists are used, they are usually stopped after 6 months unless estrogen is added to permit an additional 6 months use due to bone loss associated with GnRH agonist.

Aromatase inhibitors (anasazole) are used to treat postmenapausal breast cancer but can be used for adults with endometriosis; it may be combined with oral contraceptives or GnRh. This may be an option for women who have not had success with other treatment or are unable to use other treatment modalities.

Surgical management is also useful for many with endometriosis as noted in Table 22 and hormonal management can be continued after surgery to control the development of endometriosis that may occur after surgical treatment. Preservation of fertility is also the goal of any surgical procedure in the treatment of endometriosis.

Premenstrual syndrome

Premenstrual syndrome (PMS) includes various symptoms (see Table 23) that typically initiate during the latter luteal phase just before the onset of the menstrual flow and tend to resolve with the initiation of menstrual flow (Table 3). Most reproductive females report PMS features and up to 8% note severe emotional symptoms (i.e., anxiety, depression, failure to perfor daily activities) that meet the American Psychiatric Association's criteria for Premenstrual Dysphoric Disorder (PMDD) (25,26). Various theories are proposed for PMS, though the precise cause (s) are not known at this time (Table 24).

A careful evaluation is necessary to differentiate PMS from such conditions as chronic fatigue syndrome, anemia, diabetes mellitus, hypothyrodism, collagen vascular disorders, and others. Adding to the confusion are the various conditions that may be worsened by menstruation; these include migraine headaches, erythema multiforme, acute intermittent porphyria, rheumatoid arthritis, recurrent anaphylaxis, and the three "periodic" conditions—periodic fever, paralysis, and hypersomnia.

Table 23. 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

*Used with permission from: Greydanus De, Omar HA, Tsitsika AK, Patel DR: "Menstrual disorders in adolescent females" In: Pediatric and Adolescent Sexuality and Gynecology: Principles for the Primary Care Clinician. NY: Nova Science Publishers, Inc. ch. 7: 388-9, 2010.

Table 24. Proposed Theories for PMS

Dysfunction of serotonin or γ-aminobutyric acid A (GABA-A)
↑ sensitivity to hydroxy-tryptamine (5-HT) receptors (with ↓ with reduced levels and impaired uptake of serotonin)
Anxiety: dysfunctional interaction of metabolites of progesterone and receptors of γ-aminobutyric acid A (GABA-A) receptors
Panic Attacks: ↑ luteal phase levels of P_{CO2}
Impact of recurrent episodes with ↑ sensitization and more PMS symptoms
Complex and perplexing interplay between various chemicals and systems:
• prostaglandins, endogenous opioid peptides, serotonin (other central
• nervous system neurotransmitters), ovarian steroids, and the peripheral
• autonomic nervous system
Miscellaneous psychological factors (contributory but not primary causative)

Management of PMS

Various supportive measures are typically recommended for PMS symptoms including regular exercise, healthy sleep-wake cycles, regular hot baths, reduced salt intake, reduced intake of caffeinated beverages (often high in adolescents), improved nutrition (with less sugar), abstinence from alcohol, and reduction in excessive stress. NSAIDs may improve breast or pelvic pain noted in some with PMS, while diuretics (such as spironolactone or hydrochlorothiazide) may relieve symptoms due to PMS weight gain or edema; abuse of diuretics, however, may lead to increased weight gain from increased edema.

Measures often suggested but without supportive research include herbal or vitamin supplementation. Such 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 B6 supplementation, and supplementation with calcium or magnesium.

Management of symptomatic anxiety or depression (or mental health disorders) is important. PMS emotional features (table 23) may show some improvement with the judicious use of selective serotonin reuptake inhibitors (SSRIs), such as sertraline (50 mg daily), fluoxetine (20 mg daily), or paroxetine (20 mg daily). Those with excessive symptoms of anxiety may benefit from prescription of anxiolytics such as alprazolam or buspirone. Some clinicians have used tricyclic antidepressants (such as clomipramine), though great care should be exercised

in prescribing tricyclic antidepressants (TCAs) to adolescents due to the many side effects (27).

Measures used for adults with severe PMS include gonadotropin-releasing hormone (GnRH) agonists (such as leuprolide [Lupron] and buserelin [Suprefact]). These agents produce a medical oophorectomy by suppression of gonadotropin release with resultant prevention of ovulation and ovarian hormone production. Adult females with severe mastalgia as part of their PMS have been prescribed bromocriptine, a dopamine-receptor agonist.

Conclusion

Menstrual disorders are common in the adolescent female. This paper reviewed basic concepts of menstrual disorders in adolescents beginning with an overview of menstrual physiology followed by consideration of various abnormal menstrual patterns: amenorrhea (primary and secondary), dysfunctional uterine bleeding, dysmenorrhea (primary and secondary), and premenstrual syndrome.

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