NCC Pediatrics Continuity Clinic Curriculum:
Adolescent II: Menstrual Irregularities
Faculty Guide

Goal:

- Understanding of normal and abnormal menstruation
- Know when and how to obtain a menstrual history
- Understand how to manage common menstrual abnormalities

Pre-Meeting Preparation:

- Review Menstrual Cycle Basics with **The Menstrual Cycle 3D** *(Dr. Paulien Moyaert)*
- Read "Disorders of Menstruation in Adolescent Girls" (*Pediatric Clinics of N. America, 2015*)

Conference Agenda:

- Complete Disorders of Menstruation Quiz & Case Studies

Post-Conference: *Board Review Q&A*

Extra Credit:

- "The Impact of Irregular Menstruation on Health: A Review of the Literature" *(Cureus, 2023)*
- "Menstruation in Girls and Adolescents: Using the Menstrual Cycle as a Vital Sign" *(ACOG, 2020)*
- "Menstruation Management for Adolescents with Disabilities" *(AAP Clinical Report, 2016)*
- "Menstrual Disorders" *(PIR, 2013)*

Disorders of Menstruation in Adolescent Girls

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KEYWORDS

• Adolescent • Menstrual disturbances • Amenorrhea • Menstruation
• Dysmenorrhea • Abnormal uterine bleeding

KEY POINTS

- Distinguishing whether the teen is ovulatory or not can be helpful in narrowing the differential diagnosis.
- The menstrual cycle can take several months to become regular and ovulatory. Reassurance may be all that is necessary but treat if interfering with activities or depleting the teen (physically and/or emotionally).
- Primary physiologic dysmenorrhea is usually not present at menarche; it accompanies the establishment of ovulatory cycles. Take NSAIDs proactively and be suspicious of endometriosis if properly administered nonsteroidal antiinflammatory drugs (NSAID) in combination with Combined Contraceptives (CCs) fail to control dysmenorrhea. Similarly, be suspicious of outflow obstruction if dysmenorrhea is intractable, if menarche is painful or if puberty is near complete and no menses has occurred.
- CCs offer many benefits but teens and/or parents often have misinformation about safety and side effects that must be addressed.
- Functional amenorrhea is a diagnosis of exclusion and is caused by an imbalance of stress, diet, and/or exercise. These factors can also cause irregular menses.
- It can be difficult to identify polycystic ovarian syndrome (PCOS) patients during adolescence.
- With true menorrhagia, take bleeding history from teen and her family.

INTRODUCTION

Abnormal menstruation in adolescent girls can cause psychological, emotional, and physical strain from excess, unpredictable, painful, or even absent bleeding. This article discusses these common complaints and describes variations of normal, including the maturation of the hypothalamic-pituitary-ovarian (HPO) axis, but goes on to provide indications for reassurance alone versus active intervention. (**Figs. 1** and **2**) show broad differential diagnoses for common symptoms. It is important for readers to recognize that these key figures and their list of underlying

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Fig. 1. Abnormal uterine bleeding in adolescents: heavy, prolonged, and/or irregular (those noted with an asterisk can also present as secondary amenorrhea). CNS, central nervous system.

Fig. 2. Primary amenorrhea. GnRH, gonadotrophin-releasing hormone; MRKH, Mayer Rokitansky Kuster Hauser syndrome; PCOS, polycystic ovarian syndrome.

conditions are meant to guide the clinician's history, physical examination, and the choice of investigations. Treatment options are organized according to symptoms and presenting complaints in Table 1, which can be referenced regardless of the underlying disorder. The article elaborates on hypothalamic/functional amenorrhea, polycystic ovarian syndrome (PCOS), and primary dysmenorrhea, and applies or adapts the previously described basic principles of history, physical examination, investigations, and treatment to these conditions. To avoid missing the diagnosis, inherited bleeding disorders are discussed.

THE COMMON PRESENTING COMPLAINTS

Care providers for adolescent girls are likely to be confronted with concerns over periods that are perceived as too heavy or prolonged, too painful (dysmenorrhea), irregular (unpredictable, too frequent, or infrequent), and/or nonexistent (primary or secondary amenorrhea). There are many suggested sets of terminology but, to avoid misinterpretation, this article uses lay language descriptors and the term abnormal uterine bleeding (AUB). When it comes to heavy flow, it is often helpful to first elicit evidence of ovulation (classic premenstrual molimina such as breast tenderness, headaches, cyclic mood changes, and cycle regularity). When cycles are regular and ovulatory, but still heavy, the problem is more likely the teen's inability to manage idiopathic heavy flow or a bleeding disorder. In contrast, anovulatory cycles, or cycles triggered by infrequent ovulation, can be heavy and/or prolonged. When ovulation is absent or infrequent, the underlying cause is often endocrinopathy; imbalance or syndrome at the hypothalamus, the pituitary, or at the ovary (see Fig. 1). Infections of the lower genital tract (or a retained tampon) tend to cause intermenstrual bleeding, and pregnancy must be considered with almost every change in menstrual cycle or abnormal vaginal bleeding presentation.

Key point/pearl

- Distinguishing whether the teen is ovulatory or not can be helpful in narrowing the differential diagnosis.

Table 1
Medicinal treatment options for problematic menstrual bleeding (symptom based)

Heavy (and/or Prolonged) Flow	Irregular: Infrequent and Unpredictable	Irregular: Frequent (± Prolonged)	Painful/ Crampy
CCs	CCs	CCs	CCs
Antifibrinolytic	Cyclic oral progestins	Antifibrinolytic	—
NSAIDs (proactive)	Maybe do nothing if ≥4 cycles/y	—	NSAIDs ± acetaminophen
LAP	—	LAP	LAP
Course of oral progestin (if isolated prolonged bleed; discussed later)	—	—	—

Options need not be tried in the order listed.

Antifibrinolytics are tranexamic acid or aminocaproic acid.

Abbreviations: CCs, combined contraceptives (eg, oral pill, transdermal patch, vaginal ring); LAPs, long-acting progestins (ie, depomedroxyprogesterone acetate or levonorgestrel intrauterine system); NSAIDs, nonsteroidal antiinflammatory drugs.

WHAT IS NORMAL, AND THE MATURATION OF THE HYPOTHALAMIC-PITUITARY-OVARIAN AXIS

Although there may be trends toward earlier puberty, the average age at menarche has been fairly stable between ages of 12 and 13 years in Canada and the United States. More than 90% of adolescent girls have had menarche by 14 years of age. It is generally accepted that most menarchal bleeds are the result of endometrial proliferation from estrogen. Both thelarche and leukorrhea are evidence of estrogen exposure and precede menarche by 1 to 2 years. Menarche is an anovulatory bleed; often the result of erratic sloughing of the proliferative endometrium as opposed to a synchronous slough 2 weeks after ovulation, which explains why, for many young teens, the bleed can be prolonged and heavy but, at the same time, usually fairly painless (discussed later). It is also generally agreed that the HPO axis needs time to mature, averaging 6 months to 3 years before regular ovulatory cycles are established. The earlier menarche occurs, the sooner cycles regulate. During these months immediately after menarche, teens can experience cycles consistent with ovulatory dysfunction: irregular and unpredictable (frequent or infrequent), heavy and prolonged, but intervals between menses are seldom greater than 3 months. It is well recognized that teens and their parents may have misinformation or misguided expectations about what is normal. Education and reassurance are sometimes all that is necessary if the girl is otherwise coping. They may report her to be irregular if the cycle is not exactly every 30 days and they may report her to be experiencing heavy bleeding because she is having menstrual accidents but she is still learning how and when to use pads/tampons. Regular ovulatory cycles typically occur every 21 to 34 days and blood loss is less than 80 mL. Trying to determine which teens are experiencing abnormally heavy flow (and among them, which may have an inherited bleeding disorder [discussed later]) can be challenging. Looking for anemia and clarifying the number of saturated pads/tampons required in a day and the number/size of clots can be helpful but how it affects the girl's life is paramount. However, having to change a pad/tampon every 1 to 2 hours and greater than 7 days' moderate/heavy flow is likely excessive. Whether the teen is merely experiencing HPO axis maturation, or whether she has an underlying disorder, treatment should be indicated if the problem is causing distress or dysfunction. The American College of Obstetricians and Gynecologists' committee on Adolescent Health care has a useful summary of the menstrual cycle as a vital sign, which outlines expectations and causes for concern,[1] and Wilkinson and Kadir[2] reviewed adolescent menstrual disorders in a supplement of the *Journal of Pediatric & Adolescent Gynecology* that is dedicated to this topic and inherited bleeding disorders.

Menstrual Cramps (Dysmenorrhea)

With the establishment of ovulatory cycles, the teen may begin to experience dysmenorrhea. Primary dysmenorrhea refers to prostaglandin-mediated physiologic menstrual cramping typical of ovulatory cycles. Dysmenorrhea is typically absent from the first several menses because they are often anovulatory, and it is concerning when the menarchal bleed is very painful because it can be the result of obstructed outflow (discussed later).

Key point/pearl

- The menstrual cycle takes 6 months to 3 years on average to become regular and ovulatory.
- Reassurance may or may not be all that is necessary even if symptoms are considered a physiologic variant. Treat if interfering with activities or depleting the teen (physically and/or emotionally).

- Underlying disorders (see Fig. 1) such as disordered eating, PCOS, pregnancy, and bleeding disorders can be present during the first few years after menarche. Immaturity of the HPO axis is a default diagnosis.
- Primary physiologic dysmenorrhea is usually not present at menarche; it accompanies the establishment of ovulatory cycles.
- Helpful patient/parent information is available:
  - http://www.naspag.org/index.php/patients[3]
  - http://www.sexualityandu.ca/parents/discussing-menstruation[4]
  - http://www.youngwomenshealth.org[5]

Interpreting and Using the Figures

Fig. 1 provides a broad differential for heavy bleeding, prolonged bleeding, and/or irregular bleeding. The conditions noted by an asterisk (*) can also cause secondary amenorrhea. Secondary amenorrhea traditionally was a term reserved for cessation of menses of 6 months or more. Many clinicians now advocate for the criterion to be only 3 months or 90 days. Although there is less chance of disorder, this more lenient criterion affords more opportunity for early recognition of pregnancy, eating disorders, and so forth. Fig. 2 provides a broad differential for primary amenorrhea, which may or may not be accompanied by delayed or arrested puberty. Although definitions vary, delayed puberty in a girl refers to absence of breast development (thelarche) by age 13 years. Neither figure includes the hypothalamic-pituitary-adrenal axis, but conditions such as congenital adrenal hyperplasia, Cushing, and tumors (adrenal gland and ovary) need to be considered when there is significant androgenization/virilization or other stigmata. Chronic illness can include disorders such as type 1 diabetes, renal failure, and inflammatory bowel disease. Both hyperthyroid and hypothyroid disease can affect the HPO axis functionality and thus both figures mention thyroid endocrinopathy. Both figures list premature ovarian failure (POF), which can be idiopathic or caused by gonadal dysgenesis/agenesis (ex Turner syndrome), fragile X premutation, cancer therapies (chemotherapy, radiation), autoimmune oophoritis, and so forth. Autoimmune POF often coexists with other autoimmune conditions in the patient and/or her family. Primary ovarian insufficiency is an entity in itself but for the purposes of this article it should be considered a mild form of POF or a state of transition. Remember that these figures are meant to guide the history, physical examination, and choice of investigations.

ABNORMAL UTERINE BLEEDING: THE GENERIC ASSESSMENT

History: Key Features

- Explicit description of menstrual complaints, perceived menstrual cycle, and time elapsed since menarche: if heavy, try to establish how heavy by inquiring about the frequency required for changing pads/tampons, number and size of clots, and the duration of flow. Recall that changing pads/tampons every 1 to 2 hours and consistently greater than 7 days' heavy flow is likely excessive. If irregular, try to establish how irregular by inquiring about the longest and shortest intervals between menses. Recall that normal menses occur every 21 to 34 days and although it can take up to 3 years to establish a normal regular cycle, irregularity should prompt inquiry guided by the disorders listed in Fig. 1. For both heavy and irregular menses, try to ascertain whether the girl is ovulatory by asking about molimina such as breast tenderness, cyclic mood changes, and cramping. If painful, try to establish whether the pain is consistent with physiologic dysmenorrhea and treatments tried and how they were used (discussed elsewhere in the article). If absent (amenorrhea), establish whether it is primary (never menstruated), or secondary (>90 days warrants assessment). Other

important clues include the mother's age at menarche, any history of pelvic pain, the subjective impression of pubertal progression, and any chance of pregnancy.
- Review of systems using Fig. 1 or 2 as a guide looking for symptoms of endocrinopathy or syndromes such as dieting, thyroid imbalance, or PCOS.
- Sexual history and need for contraception.
- Traditional past medical history, past surgical history, medications, smoking/risk taking, allergies, and related family history.

Physical Examination

Depending on the presenting complaint, clinicians should use Fig. 1 or 2 as a guide when looking for physical stigmata of endocrinopathy or syndromes such as short stature (Turner syndrome), underweight (eating disorder), goiter (thyroid condition), and hirsutism/obesity (PCOS).

Physical Examination: Key Features

- Height, weight, body mass index (BMI) (calculate percentage and plot on growth chart), blood pressure (especially if the patient is obese or has PCOS features, and/or if combined contraceptives [CCs] will be prescribed).
- Secondary sexual characteristics/Tanner staging, if applicable.
- Abdominal examination.
- If menses are absent, introital examination must be included and consider single-digit vaginal examination. Is there a vagina, patent hymen, leukorrhea? Leukorrhea is suggestive of current estrogen.
- Speculum examination is not always indicated (recall, Pap smear is no longer indicated in teens, and urine can be sent for some sexually transmitted infection [STI] screening).
- If there is intermenstrual bleeding, and/or the girl is sexually active, consider a speculum examination, but, if the teen is precoital, choose a narrow speculum (if deemed necessary).

Investigations and Diagnostic Tools

It is hoped that, through history and physical examination, the differential diagnosis has been narrowed, but the clinician usually needs to choose from the following list of investigations to confirm or refute plausible conditions.

Investigations and Diagnostic Tools to Consider

- Urine human chorionic gonadotropin (HCG)
- Complete blood count, ferritin
  - Anemia might corroborate abnormally heavy flow and raise the suspicion of a bleeding disorder or add justification for treatment
- Thyroid-stimulating hormone (TSH) (free T4), plus or minus prolactin
- Follicle-stimulating hormone (FSH), luteinizing hormone (LH)
  - High (menopausal) gonadotropin levels confirm gonadal or ovarian insufficiency or failure (discussed elsewhere in the article). If LH and FSH are both less than 1 the clinician can be confident that the problem is hypothalamic or pituitary dysfunction, but often low normal values are difficult to interpret.
- Ultrasonography pelvis.
- Clinicians should individualize the need for cervix and/or vaginal swabs, and pregnancy testing. Although urine can be tested for gonorrhea and *Chlamydia*, *Trichomonas* requires a vaginal swab.
  - Examples of accessory testing to consider:

- If functional or hypothalamic amenorrhea, PCOS, or bleeding disorder is suspected, see the relevant parts of this article outlining other warranted investigations.
- If there are central nervous system (CNS) symptoms or hyperprolactinemia, consider brain imaging.
- If there is gonadal insufficiency or failure, order karyotype and consider referral (pediatric endocrine, pediatric/adolescent gynecology, genetics).
- If there is profound or marked hyperandrogenism/virilization, consider serum androgens plus or minus adrenocorticotropic hormone (ACTH) stimulation and imaging adrenals. This situation is likely to warrant referral (pediatric endocrine or gynecology).
- If there is intractable dysmenorrhea or primary amenorrhea suggestive of müllerian anomaly, consider MRI pelvis and referral (pediatric/adolescent gynecology or gynecology).

Also consider referral (eg, gynecology, pediatric gynecology, pediatric endocrine, genetics hematology, psychiatry, as indicated) for:

1. Delayed or arrested puberty
2. True eating disorder or elite athlete
3. Inherited bleeding disorder
4. Complex or confusing scenarios in which investigations or response to traditional therapies are unsuccessful

For more detailed reviews of delayed puberty, primary ovarian insufficiency, and POF in adolescents see Refs.[6–14]

Treatment (in General)

Table 1 presents a symptom-based chart of several useful medicinal treatment options that can be used and referred to by clinicians almost independent of underlying condition. The following list elaborates further on these treatment modalities and a series of questions is provided to help the clinician choose from the various reasonable medications for any particular menstrual complaint/symptom.

Treatment Options (in General)

- Nonsteroidal antiinflammatory drugs (NSAIDs): ibuprofen, mefenamic acid, naproxen sodium, ketorolac
- CCs: daily pill, weekly patch, monthly vaginal ring
  - Consider extended cycle: gradually increase the number of consecutive weeks between hormone-free intervals (HFIs), when either the HFI or the withdrawal bleed are still problematic.
  - Consider shortening the HFI when either the HFI or the withdrawal bleed are still problematic. For example, 4 days off instead of 7.
- Cyclic oral progestins: 5 to 10 mg of medroxyprogesterone acetate or 200 mg of progesterone X for 10 to 14 days. These progestins can be used to induce a withdrawal bleed in teens whose menstruation is heavy and prolonged but infrequent. A single course can also be useful as a medical dilatation and curettage for isolated anovulatory bleeds that continue for several weeks.
- Depomedroxyprogesterone acetate (DMPA) 150 mg intramuscularly every 10–13 weeks.
  - Informed choice about weight gain, side effects (including irregular bleeding or amenorrhea), bone density

- Levonorgestrel intrauterine system (LIUS)
  - Patient must be properly selected and counseled
  - Adolescent age is not a contraindication to intrauterine device or system
  - Nulligravid patients may experience more cramping and higher expulsion rate
- Antifibrinolytics: tranexamic acid 1 to 1.5 grams p.o. 3 to 4 times/d, aminocaproic acid 2 to 4 grams p.o. 4 to 6 times/d.

Consider referral when there are contraindications to CCs or for LIUS insertion.
When using **Table 1**, ask:

1. What are the symptoms of priority? Heavy? Irregular? Painful?
2. What are the patient's preconceived ideas about, and past successes/failures with, methods?
3. Can the patient/family afford it? Is subsidy available?
4. Will the patient adhere to or accept it (eg, would she take a daily pill or accept an injectable method)?
5. Are there any contraindications (eg, CCs and migraines with complex neurologic features, LIUS and current STI cervicitis)?
6. Are there any other noncontraceptive benefits to be exploited (eg, CCs and acne or hirsutism)?
7. Does the patient also need reliable family planning/contraception? Private time with patient alone should be part of the routine to allow for open discussion and to reinforce healthy sexual choices and advise dual protection (advised).
8. Does the patient also need an iron supplement?

Other key points/pearls (for treatment in general)

- NSAIDs work best if they are taken proactively (and combined when necessary with acetaminophen).
- CCs offer cycle regulation, reduced flow, reduced cramps, and reduced acne/hirsutism with a single medication, but teens and/or parents often have misinformation or misperceptions about safety and side effects that must be addressed to facilitate compliance/adherence. For example, confidently reassure that CCs do not cause significant weight gain or cancer.[15,16]
- If planning to use CCs in an extended cycle fashion, slowly increase the number of consecutive weeks between HFIs. Continuous use from the outset often involves persistent breakthrough bleeding that frustrates the teen and leads her to abandon the treatment plan.
- There is still a role for DMPA in properly selected and fully informed adolescents.
- Pelvic examination is not a prerequisite for hormonal methods (except intrauterine).

ABNORMAL UTERINE BLEEDING: CAUSES WORTHY OF PARTICULAR MENTION

Functional hypothalamic amenorrhea, PCOS, dysmenorrhea and inherited bleeding disorders.

Functional Hypothalamic Amenorrhea (and Disordered Menstruation)

Functional (hypothalamic) amenorrhea refers to the absence of menses as a result of an imbalance of stress, dietary intake, and exercise. With respect to dietary intake and exercise, it is generally accepted that there is insufficient nutritional intake to match the energy expenditure, thus resulting in a deficit. Eating disorders or disordered eating are common but not always present, and weight loss may have occurred but is not

a necessity. Gonadotrophin-releasing hormone ceases to pulse effectively (if at all) and the HPO axis gets suppressed or becomes ineffective. The patient's presentation depends on when the problem is acquired in relation to puberty and menarche, and how severe the extremes of diet/stress/exercise are. The patient may present with delayed puberty or arrested puberty and primary amenorrhea but secondary amenorrhea is far more common and consistent. Disordered menstruation with irregular or infrequent cycles can occur initially or when the imbalance is less severe. Catherine Gordon[17] has written an outstanding review of hypothalamic functional amenorrhea for the *New England Journal of Medicine*.

When the teen presents with delayed menarche (primary amenorrhea) the health care provider must consider other differential diagnoses such as (but not limited to) Kallmann syndrome (hypothalamic), POF (gonadal), or a müllerian anomaly (outflow tract) (see **Fig. 2**). Obstructing anomalies such as imperforate hymen and transverse vaginal septum should be easy to eliminate with a mini–genital examination, especially if there is no history of pelvic pain despite significant pubertal development. **Fig. 3** shows some of these anomalies, but more detailed reviews of müllerian anomalies (obstructive and nonobstructive) were published as clinical recommendations in the *Journal of Pediatric & Adolescent Gynecology* December 2014.[18,19] Vaginal agenesis [Mayer Rokitansky Kuster Hauser (MRKH) syndrome] can exist with or without a uterus and that uterus may or may not have a nidus of functional endometrium. Thus, whereas/although vaginal agenesis always presents with normal puberty, there may or may not be any pelvic pain complaints. If there is little or no pubertal development, attention should be focused on hypothalamic and ovarian causes (see **Fig. 2**).

Clues on history corroborating functional/hypothalamic disorder

Patients often report that cycles were regular and then disappeared or became very infrequent (sudden or gradual). Inquiry might identify weight loss, eating disorder, psychosocial stress or anxiety, performance pressure, and exercise for health, weight loss, or competitive athletics. A validated eating aptitudes test could be used.[20]

Health care providers who care for teens should make regular inquiries about the presence of menstrual cycles and consider this a fifth vital sign.[1] Similarly, diet, exercise, and body image are important topics for routine inquiry. Teens who are not menstruating may not be acquiring bone density at the intended rate. Although there

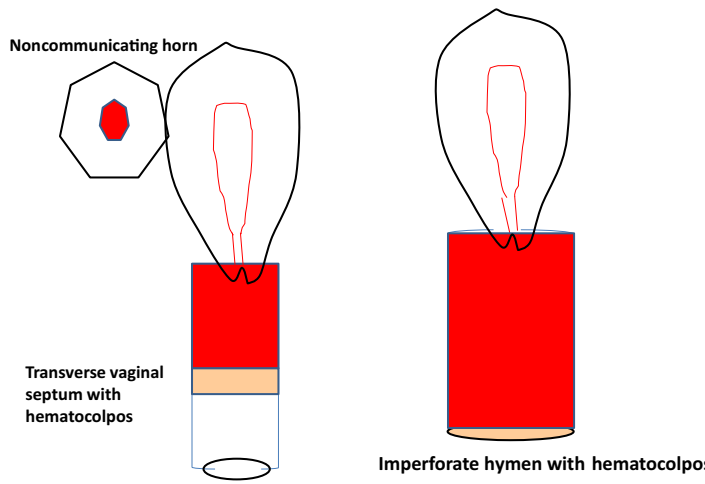

Fig. 3. Examples of obstructive anomalies.

can be denial and a lack of insight, pressing for a detailed dietary log and exercise schedule plus exploring psychosocial stressors and anxiety is important in recognizing and confidently diagnosing functional/hypothalamic amenorrhea.

Clues on physical examination corroborating functional/hypothalamic disorder BMI tends to be low. Look for signs of eating disorders and compensatory behaviors, absent or arrested puberty, and absent estrogen at introitus (eg, red hyperemic, tissues less plump, few rugae). None of these features are compulsory in making the diagnosis but be sure to rule out signs of other endocrinopathies or syndromes (see **Figs. 1** and **2**), such as hyperthyroidism or hypothyroidism and PCOS or a true eating disorder. Eating disorder reviews provide extensive lists of stigmata.[21,22]

Clues from investigations that corroborate functional/hypothalamic disorder Clues include low or undetectable FSH level and low or undetectable LH level, although other investigations, such as TSH, prolactin, and pelvic ultrasonography, will be normal. Once the diagnosis is made, other investigations may be indicated, such as bone density or complete blood count.

Management of functional/hypothalamic amenorrhea

Clinicians should also focus on the menstrual complaints and symptoms and use the guide to general treatment options in **Table 1**. For example, if the teen has stress-related or diet-related unpredictable and infrequent menses, she could use CCs or cyclic progestins (if she does not need birth control), but this does not address the causative imbalance.

For functional hypothalamic amenorrhea (or disordered menses), the patient needs to understand her condition and be motivated to make changes. She may need counseling or strategies to deal with stress, or more likely she will need to increase caloric and nutritional intake or reduce the amount of vigorous exercise she is doing. A consultation and follow-up with a dietician (who has some understanding of this condition) may increase the likelihood of resumption of menses, but the patient should know that it can take some time. Multidisciplinary care may be warranted, especially if there is an underlying eating disorder, an anxiety disorder, or elite athleticism. There is still debate about whether a critical weight or body fat percentage needs to be reached, but, if weight loss was involved in the original cessation of menses, the teen may need to regain that weight and a bit more. Bone health is at risk while the amenorrhea persists and CCs have not been shown to be protective in this setting. This author finds it helpful to conceptualize when explaining this condition and recovery to patients and their parents. Explain that the brain is unwilling to allow fertility until it is convinced that it can trust the adolescent to provide it with regular adequate nutrition (no deficit) and that she is coping better with life. This concept seems to make sense in its simplicity but the addendum always worth mentioning to teens who are (or are going to become) sexually active is that it is not a reliable form of pregnancy prevention.

Key points/pearls

- Functional hypothalamic amenorrhea is a diagnosis of exclusion and is caused by an imbalance of stress, diet, and/or exercise.
- Hypothalamic or brain issues can cause ovulatory dysfunction without necessarily being severe enough to completely suppress the HPO axis. These causes can present with irregular bleeding or amenorrhea.
- Be suspicious if the patient is fully pubertal but has not experienced menarche; ask about pelvic pain, which might signify obstructive müllerian anomaly or müllerian agenesis.

- There are 2 specific groups worthy of mention but that are beyond the scope of this article: the female athletic triad and patients with eating disorders (especially anorexia). When exploring history and performing physical examination for amenorrhea and/or disordered menses, health care providers may identify one (or both; they can coexist) of these diagnoses. The female athletic triad refers to absent menses in an athlete with osteopenia and low energy availability (imbalance of nutrition vs energy expenditure but not always with coexistent eating disorder).
- Select articles are provided and recommended for more detailed review of eating disorders.[21–23] Dr Catherine Gordon's[17] review of functional amenorrhea mentions the athletic triad and Youngwomenshealth.org has patient information on this condition at http://youngwomenshealth.org/2010/05/21/female-athlete-triad/.

Polycystic Ovarian Syndrome

It is now well recognized that PCOS occurs in adolescents, and may begin during childhood or earlier. Typical features/stigmata (not all present in all patients) include obesity, menstrual disturbances, hyperandrogenism, insulin resistance, metabolic syndrome, and polycystic/enlarged ovaries.[24–27] There is a familial tendency that probably results from both genetic and environmental influences. Because puberty, and specifically the first couple of years after menarche, can be a time of hyperestrogenism, hyperandrogenism, and oligo-ovulation, manifesting as irregular menses and acne, the subgroup of adolescent girls who will ultimately be diagnosed with PCOS can be difficult to identify (without incorrectly diagnosing some girls who are merely peripubertal and perimenarchal). Complicating matters is the current epidemic of childhood and adolescent obesity. Although obesity is not a mandatory feature of PCOS, it is present in a significant percentage of girls with PCOS, but this feature has become less discerning as average body weight and BMI has increased alarmingly in North America. Several groups have tried to create and impose diagnostic criteria to unify researchers and the literature for a better understanding of PCOS and to try to validate diagnoses. The most rigorous and selective of the diagnostic criteria schemes specific to adolescents is that put forth by Carmina and colleagues.[28] This definition requires that the teen be at least 2 years postmenarche and have both hyperandrogenism (as shown by acne, hirsutism, alopecia) and oligo-ovulation (<6 cycles per year). In this situation, PCOS is highly likely but, with these criteria, diagnosis is considered absolute if ovaries on ultrasonography show the classic polycystic look or increased ovarian volume. Carmina and colleagues'[28] criteria take into account the normal physiologic changes of early adolescence and the significant overlap between normal peripubertal (perimenarchal) ovaries and classic PCOS ovaries. In contrast, by insisting on 2 years postmenarche, diagnosis could be delayed for some teens, and not all experts support the requirement of ultrasonography features.

A subset of patients with PCOS have metabolic syndrome, which usually involves obesity but specifically refers to hypertension, insulin resistance, glucose intolerance/type II diabetes mellitus, and dyslipidemia. Another subset of patients with PCOS present with primary amenorrhea but these teens tend to be hyperandrogenized and more investigations may be indicated to rule out other conditions.

Consider referral to either a multidisciplinary team or a pediatric endocrinologist and a cardiologist if metabolic syndrome is suspected. Consider referral to a subspecialist if the teen presents with primary amenorrhea and presumed PCOS.

Clues on history that corroborate polycystic ovarian syndrome

Patients often report that cycles are irregular (frequent or infrequent), heavy, and seldom painful (except when there are large clots or occasionally when the patient

is ovulatory). She could also be amenorrheic. Inquiry might identify unexplained excess weight gain at puberty, acne, and hirsutism.

Clues on physical examination that corroborate polycystic ovarian syndrome BMI tends to be high, and there could be increased blood pressure, acne, hirsutism (consider Ferriman-Gallwey score for charting hirsutism). There should not be true virilization. There may be dark, velvety, dirty-looking skin in creases (acanthosis nigricans) and boils in vulva/groin or axilla (hidradenitis suppurativa). Be sure to rule out signs of other endocrinopathies or syndromes (see **Figs. 1** and **2**) such as hypothyroidism, Cushing syndrome, or another androgen disorders causing marked virilization.

Clues from investigations that corroborate polycystic ovarian syndrome, and investigations to consider Normal FSH and LH levels, but possibly LH/FSH ratio greater than 2; normal TSH and prolactin levels; high fasting insulin level; fasting glucose/fasting insulin ratio less than 4.5; high 2-hour sample after 75-g glucose challenge (to be preceded by 12-hour fast and to include fasting glucose and fasting insulin); abnormal fasting lipid profile (high triglyceride level, low HDL level), and mild increase of total testosterone level (discussed later).

Comment It is this author's opinion (shared by some invesigators[29,30] but not by others[25,28]) that serum androgens are not often indicated in the diagnosis of PCOS or the setting of typical hirsutism. If there is marked hyperandrogenism or true virilization (and/or rapid onset/progression), then serum androgens (fasting 17-OH progesterone, plus or minus ACTH stimulation, testosterone (total and free), dehydroepiandrosterone sulfate, androstenedione, and imaging of ovaries and adrenal glands may be indicated, but this is in the extreme and rare setting and warrants referral.

Management of polycystic ovarian syndrome

Readers are also reminded to focus on the menstrual complaints and symptoms, to use **Table 1**, and to refer to this article's discussion of treatment options in general. For example, if the teen has heavy menses, she could use antifibrinolytics, but if she also has unpredictable menses and acne/hirsutism she may want to choose CCs; however, this does not address the need for healthy diet and exercise and achieving or maintaining ideal body weight. For an adolescent girl with PCOS, the agenda is more likely to be to gain control of acne, hirsutism, menstrual irregularity, or flow, and the girl's weight. The patient (or their parents) may also be concerned about future fertility. Ideally the health care provider educates and motivates the teen and her parents in order to avoid the recognized comorbidities and future health issues that patients with PCOS can experience: obesity and type II diabetes (and their sequelae, such as heart disease and sleep apnea), endometrial hyperplasia or malignancy, and psychological distress/poor self-esteem.

First and foremost, healthy diet and exercise need to be achieved. This goal is easier said than done, especially for teens. Teens may be more motivated if they are aware that even modest weight loss can be associated with improvement in their PCOS symptoms, such as menstrual disruption, acne, and hirsutism. While maximizing results through lifestyle, CCs (oral, transdermal, or vaginal) tend to be one of the main therapeutic modalities to achieve both menstrual management and reduced hyperandrogenism (plus pregnancy prevention where necessary). The role of insulin sensitizers in these teens is still a topic of intense debate and controversy, but this author has yet to be convinced they have a role in nondiabetic teens with PCOS.

Polycystic ovarian syndrome, combined contraceptives and venous thromboembolism in adolescents

It is generally accepted that the likelihood of experiencing a VTE event on CC (as an independent risk factor), is increased 2-fold to 3-fold. However, for most teens without an inherited tendency or thrombophilia such as factor V Leiden deficiency, the baseline absolute risk is extremely low (in the order of 1 to 2 per 10,000 woman-years), but hyperandrogenism and obesity (and smoking) are also independent risk factors. However, it is important to recognize that, without an inherited thrombophilia, the likelihood of a VTE event on a CC, regardless of progestin, even in an obese teen with PCOS, is not likely to be much higher than 1 in 1000 and is far lower than the risk associated with pregnancy/postpartum in that same teen.[31–37]

Key points/pearls

- Suspect PCOS if there is irregular (often infrequent) menses, hirsutism/acne, and tendency to easy weight gain.
- It can be difficult to select out patients with PCOS from those who are merely manifesting perimenarchal adolescent physiology.
- Diet, exercise, and maintenance of healthy body weight are paramount.
- CCs often address the adolescent's agenda (menstrual regularity, acne, and hirsutism).
- Risk of VTE on CCs is higher in teens with PCOS and obesity, but VTE is still a rare event unless there is a coexistent inherited thrombophilia.

Dysmenorrhea (Menstrual Cramps)

Primary dysmenorrhea is physiologic prostaglandin-mediated menstrual cramping. It tends to be midline and low pelvic, and sometimes radiates down legs or around to the low back. It is not usually present with the menarchal bleed. Gradually, over the months or few years postmenarche, as the HPO axis matures, cycles become ovulatory and more regular and with this comes primary dysmenorrhea of variable severity. Sometimes adolescents report that NSAIDs failed, but they were waiting too long. Other causes of menstrual cramping include (but are not limited to) endometriosis and cyclic constipation. Endometriosis most definitely does occur in adolescents and has been reviewed by several investigators recently.[38–42] There can be a family history, but the most common manifestations are intractable dysmenorrhea that eventually fails to respond to usual treatment strategies (discussed later), chronic pelvic pain, or deep dyspareunia. When the teen fails to respond adequately to NSAIDs (plus or minus acetaminophen) or when the teen also needs reliable family planning, hormonal contraception is the next strategy, along with a discussion of healthy sexual choices and dual protection. See this article's discussion of treatment options in general and **Table 1**.

Caution

When menarche is accompanied by severe pain, suspect a menstrual outflow obstruction. The most likely obstructive müllerian anomaly that would still allow menarchal flow is a noncommunicating uterine horn (see **Fig. 3**). In addition, be aware of teens who seemingly are premenarchal but have well-developed secondary sexual characteristics and are experiencing episodes of severe pelvic pain. An obstructive anomaly such as transverse vaginal septum, imperforate hymen (see **Fig. 3**), or vaginal agenesis (with uterine remnant) must be ruled out. For a detailed description of both obstructive and nonobstructive müllerian anomalies, consult the North American Society of Pediatric and Adolescent Gynecology (NASPAG) 2014 clinical recommendations.[18,19]

Refer to pediatric adolescent gynecology (or gynecology) when anything other than primary physiologic dysmenorrhea is suspected or when treatments are failing to control the menstrual pain.

Key points/pearls

- Be proactive with cramp medications. Combine acetaminophen with NSAIDs.
- Be suspicious if properly administered proactive NSAIDs (plus or minus acetaminophen) in combination with CCs fail to control dysmenorrhea.
- Consider endometriosis if there are other features of pelvic pain and dyspareunia.
- Be suspicious if there is significant pubertal progress but no menarche, especially if there is recurrent pelvic pain (müllerian anomaly).
- Be suspicious if the menarchal bleed is very painful (consider obstructive müllerian anomaly).

Inherited Bleeding Disorder

The most common inherited bleeding disorders in women include von Willebrand disease (VWD), symptomatic hemophilia (type A is factor VIII deficiency and type B is factor IX deficiency), platelet dysfunction, and other factor deficiencies (eg, VII and XI). It is estimated that up to 1 in every 5 women and girls with true menorrhagia (abnormally heavy flow) have an inherited bleeding disorder and most have VWD. Many of these bleeding diatheses have well-known inheritance patterns and ideally the diagnosis is made before menarche. However, this is not often the scenario. Menarche is often a time when the diagnosis is made after the girl has suffered psychologically, socially, and physically while trying to contend with her first menstrual cycle (or the first several). It is important to determine whether the girl has had other challenges with hemostasis, such as nose bleeds, gum bleeds, joint bleeds and bruising, excess bleeding with wisdom teeth extraction, or tonsillectomies, and this is the time to actively seek out the mother's menstrual and obstetric history and the family history of bleeding (eg, postpartum hemorrhages, anemia and heavy menses, the need for early hysterectomies). However, an absent family history does not exclude the diagnosis. For more information about abnormal menstruation caused by bleeding diatheses, the reader is referred to several outstanding reviews.[2,43–52]

Much effort has gone into trying to develop tools that will assist clinicians in selecting out those women and girls who warrant investigations for a bleeding disorder. These tools have included pictorial blood assessment charts (which are not always on hand and practical) and bleeding scores or questionnaires, and some have specifically examined children and teens.[53–56]

Key points/pearls

- Take bleeding history from teen and her family.
- Consider screening for inherited bleeding disorder if the patient reports one of the following:
  - A duration of menses greater than or equal to 7 days plus flooding or impairment of daily activities with menses
  - A history of treatment of anemia
  - A family history of a diagnosed bleeding disorder
  - A history of excessive surgical bleeding or obstetric (and gynecological) bleeding complications in teen or parent (ask specifically about tonsils/adenoids and dental extraction)

Investigations to be considered (in addition to those listed earlier)

- Peripheral blood smear
- Prothrombin time (PT), activated partial thromboplastin time (aPTT)
- International Normalized Ratio (INR) and thrombin time (TT)
- Renal and liver function tests
- ABO blood group
- VWF:Ag, VWF:RCo, FVIII*

However, there are many conditions and situational factors that can affect the test results, such as stress, acute bleeding, blood type O, and hyperthyroidism, so consultation with a hematologist is recommended to assist with making the diagnosis, interpretation of results, and/or additional testing. Be aware that many patients with an inherited bleeding disorder have normal PT, PTT, INR, and TT.

Treatment strategies for nonacute heavy menstrual flow in adolescents with an inherited bleeding disorder are identical to those described for treatment options in general and in **Table 1**. For example, heavy flow but migraines with focal neurologic features in a teen who has an inherited bleeding disorder but also needs reliable birth control might warrant a long-acting progestin. If intramuscular injections are used, prolonged pressure on the injection site may be needed. If an LIUS is inserted, the expulsion rate may be higher than usual.[57] If NSAIDs are to be used for dysmenorrhea, the hematologist should know and they should be used for only a couple of days each month to avoid aggravating hemostasis with platelet dysfunction. Sometimes hematologists prescribe desmopressin acetate (DDAVP) if the teen is a DDAVP responder.

PREGNANCY

Whenever a teen presents with a change in her menses, absent or atypical, astute clinicians always take a sexual history and have a low threshold for pregnancy testing. Pregnancy may be intrauterine or ectopic and viable or nonviable.

SUMMARY

Teens present with a variety of menstrual complaints, including heavy, irregular, painful, or absent flow. Using the hypothalamic, pituitary, ovarian, and outflow tract axis as a guide, most underlying conditions are identified and can easily be managed. Sometimes reassurance is all that is necessary but treatment is indicated if/when the symptoms are causing distress or dysfunction. NSAIDs and CCs tend to be first-line modalities. Immaturity of the HPO axis, hypothalamic factors (diet, stress, and exercise), functional amenorrhea, idiopathic anovulation, and PCOS are the most common causes, but astute clinicians never overlook inherited bleeding disorders or the possibility of pregnancy.

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Adolescent II Quiz:

1. Based on the average age ranges for "normal female puberty," how would you define **precocious puberty**? Any physical signs of puberty before age 8 (newer criteria suggest cutoffs of 7 for Caucasian girls and 6 for African American girls, but this is controversial). How would you define **delayed puberty**? No physical signs of puberty by age 13.

2. Clang associations: Match the following H&P findings with appropriate cause of amenorrhea:

(A) Hirsutism or acne	PCOS (normogonadotropic/hyperandrogenic)
(B) Short stature	Turner's Syndrome (hypergonadotropic)
(C) Psychosocial stressors	Hypothalamic or ED (hypogonadotropic)
(D) Galactorrhea	Hyperprolactinemia *(multiple causes)*
(E) Striae & central obesity	Cushing's disease (normogonadotropic)

3. What is the **female athlete triad**? **Disordered eating, amenorrhea, & osteoporosis**. Eating habits can be simply irregular (e.g., skipping meals or small frequent meals) and not necessarily include maladaptive weight loss behaviors or body image issues.

4. What is the primary treatment for **PCOS**? **Weight loss** (can lower androgen levels, improve hirsutism, normalize menses, and decrease insulin resistance). Use of OCPs can help maintain a normal endometrium and Metformin can reduce insulin resistance. There is conflicting evidence that Metformin may be helpful for weight loss for some women with PCOS. Antiandrogenic medications can help if hirsutism alone is a concern, but topical and other cosmetic therapies for hair removal can also be tried.

5. Why is primary dysmenorrhea often absent during the 1st several years of menstruation? Because dysmenorrhea is typically associated with ovulatory cycles, and many adolescents experience **anovulatory cycles** during the 1st 2 years as the H-P-O axis matures.

6. Which of the following are risk factors for dysmenorrhea?

(A) BMI at 90th %ile
(B) Menarche at age 9
(C) Menstrual flow requiring q2hr pad or tampon changes
(D) Smoking (studies show may be *less* likely to experience dysmenorrhea)
(E) Mother and grandmother with h/o dysmenorrhea

7. What are the 2 mainstays of treatment for dysmenorrhea and how do they work?

(A) OCPs: Inhibit ovulation→ inhibit progesterone release→ inhibit prostaglandin synthesis→ decrease prostaglandin/leukotriene inflammatory cascade.
(B) NSAIDs: Inhibit cyclooxygenase→ reduce prostaglandin production→ reduce infl'y cascade

Adolescent II Cases:

Case 1:
A 16 year old female comes to your clinic complaining of "painful periods". She has had increasingly severe pain that begins less that 1 day before menstrual flow and typically is worst on the first 2 days of flow. She reports having to change her pad every 3-4 hours during the day. She is sexually active with her boyfriend only and "tries to remember" to use condoms for contraception. Vitals are normal for age.

What additional history would you want to elicit?
- How bad is the **pain** on a scale of 1-10? Where is it located? What is its quality? How does the pain affect her life? (school, work, social)
- Are there any "moliminal"/ **PMS symptoms**? Breast tenderness, bloating, nausea, headache?
- **ROS** which might suggest a non-GYN disorder – IBD, IBS, muscle pain; a dysmenorrhea "mimic"—PID, ovarian cyst; or a cause for secondary dysmenorrhea—congenital anomaly?
- Has she tried any **OTC medications** for pain? If so, when does she take them in relation to her cycle? Is she taking the appropriate dosage? Is she taking them scheduled or PRN?
- **Nutrition history**? Body image?

Is the patient's history more consistent with primary or secondary dysmenorrhea?
Primary—pain begins a short time before menstrual flow, is most intense on the 1st or 2nd day of flow, and resolves before the end of menstrual flow. *(Secondary—pain begins several days to 1-2 wks prior to onset of bleeding and may persist through end of menstrual flow; due to organic disease).*

Would you complete a bimanual pelvic examination on this patient? Why or why not?
- A **'modified pelvic exam'** can be offered to patients with typical primary dysmenorrhea alone (e.g. external GU exam) and should be performed for specific clinical indications.
- For s/s of PID (fever, nausea, abdominal pain, vaginal discharge; fever or lower abdominal tenderness), a **bimanual exam** is needed to assess for cervical motion or adnexal tenderness.
- *This patient does not need an internal exam* if she presents with a hx of typical dysmenorrhea with no current abdominal pain or other symptoms concerning for PID. She can still be tested for STI's through blood or urine tests, given her history of unprotected encounters.

The following additional information becomes available: Bimanual examination reveals no tenderness of the uterus, posterior cul-de-sac, or adnexae; her Tanner staging and genital examination is normal. Other physical findings include pale conjunctiva and 4-5 closed comedones on her chin and forehead.

What is the most likely diagnosis or diagnoses? Why?
- Pelvic pain: Consider primary dysmenorrhea, fibroids, ovarian cyst, endometriosis
- Other: Consider anemia (excessive bleeding?); acne vulgaris (*see Adolescent III*).

What labs, if any, will you obtain?
No labs related to likely diagnosis of primary dysmenorrhea. BUT . . .
- Consider **screening CBC** particularly if periods are heavy, as iron deficiency anemia is common in menstruating adolescent females.

Case 2:

You are the clinic PGY3 and are assigned to precept one of the eager Sub-I's. At the end of the day, you review the following HPI for co-sign:

> 15.5 yo female presents for school physical. Parental concern for missed menses x 1 year. Menarche age 13, with regular periods for approx 6 months. Then became irregular, skipping 1-2 months at a time. Usually lasted 7 days, with three pad or tampon changes daily. No spotting or dysmenorrhea. After 1 year of 'irregular' periods, had 1 year of amenorrhea. 3 days ago, had one day of very light bleeding that she hardly could consider a period. No vaginal discharge, sexual activity, dysuria, or changes in bowel habits.

Based on the Sub-I's history, does the patient have primary or secondary amenorrhea?

Secondary— absence of menses for 3 months in women with previously normal menstruation and for 9 months in women with previous oligomenorrhea. *(Remember, though, that the 1st 2 years of an adolescent's menstrual cycle can be irregular due to anovulatory cycles).*

What additional historical information should the Sub-I have documented and *why*?

Table 2. **SCOFF Questions***

Do you make yourself sick because you feel uncomfortably full?
Do you worry that you have lost control over how much you eat?
Have you recently lost more than one stone (14 pounds [6.3 kg]) in a 3-month period?
Do you believe yourself to be fat when others say you are too thin?
Would you say that food dominates your life?

* Each "yes" = 1 point; a score of 2 points indicates a likely diagnosis of anorexia nervosa.

- HEADSS interview: Is she stressed? Dieting/purging? Depressed? Sexually active? – may elicit pregnancy, hypothalamic amenorrhea (e.g. due to stress), eating disorder
- The SCOFF screening tool (left) can be used to identify risk for an eating disorder.

- Endocrine symptoms: Hirsutism, acne, voice deepening, acanthosis nigricans; changes in hair/nails, hot/cold intolerance— may suggest PCOS; hypothyroidism.
- Neuro symptoms – headache, galactorrhea, vision change— may suggest prolactinoma.

Reading further, you see the following additional history documented by the Sub-I:

> ROS:
> -no hirsutism, deepening of voice, or changes in acne pattern
> -no headaches, changes in vision, galactorrhea
> -no hot/cold intolerance, changes in skin or nails, rashes, or diarrhea/constipation.
>
> HEADSS:
> -**H:** lives with step mother, father, and 4 siblings; real mother lives in California; approx 16 months ago real mother initiated legislation for custody of patient; patient wants to live with her mother
> -**E:** 9th grade, A/B student, feels safe at school and home
> -**A:** works out 3 days per week, has good social support, enjoys hanging out with friends
> -**D:** no depressive symptoms, sleeping 7-10 hours per night without problems, no drugs/EtoH/herbals

-**S:** no sexual activity, no suicidality
-**Diet history**: Multiple attempts to lose weight in the last year. Tries a diet for 1 week, gets bored and goes off of it for 3-5 weeks before starting a new diet. During her 'on diet' weeks, she also increases her physical activity to 4-5 days per week, 1 hr each session. She denies weight loss in the last year.

You had previously completed your own physical exam on the patient, which showed normal vital signs, including BMI, and an unremarkable physical exam with Tanner 4 breast and pubic hair and no acne, hirsutism, or acanthosis nigricans. She appears skinny but weight has been tracking with BMI at 40%le over the past 2 years.

What is your working diagnosis?
Consider causes of **secondary amenorrhea:**

- Pregnancy; Hypothyroidism; Hyperprolactinemia
- Normogonadotropic amenorrhea (e.g. **PCOS**)
- Hypergonadotropic hypogonadism (e.g. premature ovarian failure)
- Hypogonadotropic hypogonadism (e.g. eating disorder, chronic illness, **hypothalamic amenorrhea due to excessive weight loss, exercise, or stress**—*most common cause*)

What labs, if any, will you obtain?
See **Secondary Amenorrhea Algorithm**. (*Algorithm shows stepwise approach, but many providers obtain the labs in concert to expedite the work-up.)* The following is per Dr. Vogt:

First Line Tests:

- Pregnancy test, TSH, prolactin.
- LH/FSH: To distinguish hyper vs. hypogonadotropic hypogonadism. Can also see an elevated LH: FSH ratio in PCOS, but this is not very sensitive.
- Testosterone (free + total): To help diagnose PCOS. Free can be elevated in PCOS even with normal total T. Also can be elevated with minimal physical signs of hyperandrogenism.

Second Line Tests:

- Estradiol: To identify hypogonadotropic hypogonadism (assay isn't very good, though)
- DHEAS, 17OHP: If significant hirsutism or other signs of hyperandrogenism. DHEA-S can support diagnosis of PCOS or r/o adrenal tumor; 17OHP can r/o CAH.
- CBC, CMP, U/A: If clinical signs point towards chronic disease.
- Pelvic Ultrasound: If tumor is suspected.
- Progesterone withdrawal test (progestogen challenge): MPA 10mg x 10 days to test for presence of adequate estrogen exposure to build up the uterine lining. Can narrow differential, but many skip this step.

How will you manage this patient?
Treatment depends on underlying cause. For hypothalamic amenorrhea, OCPs may help promote regular menses if she desires predictable monthly cycles.

Flashback: **What nutritional deficiencies is she at risk for and how would you address?**
Adolescent females with continued amenorrhea are at risk for bone loss. Recommendation for 1000 mg calcium/day and 600 IU Vitamin D/day.

Adolescent II Board Review:

1. A 15-year-old girl is concerned about irregular menses and acne. Menarche was at age 11 years and 9 months, and she remembers developing pubic hair around age 7 years. On physical examination, her vital signs are normal and her body mass index is 32.3 kg/m2. She has facial comedonal and papular acne as well as mild darkening of the skin of her neck and axilla. You also note hypopigmented, narrow stretch marks on her abdomen and hair in a linear distribution from her umbilicus to the pubic symphysis and on the upper inner surface of her thighs. She is at Sexual Maturity Rating 5, and clitoral diameter is 2 mm.

Of the following, the MOST likely diagnosis is
A. Cushing syndrome
B. hypothyroidism
C. metabolic syndrome
D. physiologic anovulation
E. polycystic ovarian syndrome

The presence of acanthosis nigricans combined with obesity (body mass index >30 kg/m2), acne, and some increase in body hair described for the girl in the vignette as well as irregular menses 3 years after menarche suggests the need for further evaluation for polycystic ovarian syndrome (PCOS). The diagnosis of PCOS, using the 2003 Rotterdam criteria, requires, in addition to exclusion of related conditions, the presence of two of the following three criteria: 1) oligo- or anovulation, 2) clinical or biochemical signs of hyperandrogenism, and 3) polycystic ovaries. Oligo- or anovulation presents as irregular menses, and hyperandrogenism may present as acne, increased body hair, and rarely, clitorimegaly (a transverse clitoral diameter greater than 3 mm). The severity of hirsutism may be assessed using the Ferriman-Gallwey Scoring system. A score ranging from 0 (no hair) to 4 (frankly virile [extensive hair growth]) is assessed for each of nine body areas most sensitive to androgens. These sites include the upper lip, chin, chest, abdomen, suprapubic region, arms, thighs, upper back, and lower back. A score of 8 or more is considered significant and suggestive of increased androgen concentrations. The severity of acne and hirsutism, however, may not correlate well with the concentrations of androgens because the response of the androgen-dependent follicle to androgen excess varies considerably between and within persons. Therefore, total and free testosterone measurement may be supportive.

A number of risk factors for PCOS have been outlined at various stages of development. One of these factors is premature adrenarche, which is the appearance of pubic hair before age 8 years without other evidence of puberty. Whether peripubertal obesity predisposes to PCOS remains to be determined. Those who have risk factors for insulin resistance such as acanthosis nigricans or a family history of type 2 diabetes and cardiovascular disease may be at increased risk for PCOS. Acanthosis nigricans is a velvety hyperpigmentation and thickening of the skin on the nape of the neck, axilla, and other body folds. It is a nonspecific sign of insulin resistance.

A number of disorders may be considered in the differential diagnosis of PCOS but are not associated with signs of androgen excess. Patients who have hypothyroidism may be overweight and have menstrual disturbances, but they typically have other symptoms, including hair loss, constipation, and dry skin. A common symptom of Cushing syndrome is sudden weight gain. In addition, affected patients have signs or symptoms of cortisol excess such as muscle weakness; facial rounding and plethora; easy bruising; and multiple wide, purplish striae on the abdomen, not the narrow hypopigmented type exhibited by the patient in the vignette. In addition to central obesity and high blood pressure, patients who have metabolic syndrome have elevated fasting glucose and triglyceride values and decreased high-density lipoprotein cholesterol values. Metabolic syndrome is common in those who have PCOS, and such patients should be screened

regularly for metabolic syndrome. Physiological anovulation becomes less likely as an explanation for irregular menses 3 years after menarche.

2. A 15-year-old girl complains of significant pain with her monthly menstruation that results in her missing school for 1 day each month. The pain is worse on the first day and subsides spontaneously over the next 2 days. She has tried ibuprofen and naproxen sodium with no relief. On physical examination, you note pustular acne diffusely over her face and trunk. Other findings are normal.

Of the following, the medication that is MOST likely to be of benefit for both of this girl's problems is
A. acetaminophen
B. diuretic with menses
C. isotretinoin
D. omega-3 fatty acids
E. oral hormonal contraception

Hormonal methods of contraception are associated with health benefits beyond pregnancy prevention. An understanding of the noncontraceptive benefits of these birth control methods can increase compliance and continuation of use, thus decreasing unplanned pregnancy. The noncontraceptive benefits include a decrease in ovarian cyst formation as well as ovarian, endometrial, and colorectal cancer. They offer some protection against salpingitis and ectopic pregnancies and decrease benign breast disease and acne. They also decrease dysmenorrheal and menorrhagia, reduce iron deficiency anemia and osteoporosis, and decrease the symptoms of polycystic ovarian syndrome. Accordingly, the girl described in the vignette may experience relief of her dysmenorrhea and some improvement in her acne with oral hormonal contraception.

Diuretics have been used for the treatment of bloating and weight gain associated with menstruation. Spironolactone, a potassium-sparing diuretic and androgen receptor blocker, has achieved the greatest popularity, largely as a result of specific properties that make this agent uniquely suited to hormonally based disorders. Other diuretics have been tried for treatment of premenstrual syndrome, with variable success in alleviating water retention symptoms. However, diuretics are not effective in the management of dysmenorrhea. Acetaminophen does not target the prostaglandins causing menstrual cramps. Early evidence suggested possible benefits of fish oil/omega-3 fatty acids for women who have dysmenorrhea, but further studies are required to confirm these findings. Isotretinoin is indicated for nodular acne or severe acne that is unresponsive to conventional therapies but would not improve dysmenorrhea.

3. The mother of a 12-year-old white girl is concerned because her daughter has not yet menstruated. Most of her daughter's classmates are menstruating. She does not remember when her daughter began breast development but states that the girl is now taller than her 13-year-old brother. The mother asks if you can estimate when her daughter is going to have her first menstrual period.

Of the following, the MOST appropriate next step to answer the mother's question is to
A. determine bone age
B. determine Sexual Maturity Rating
C. measure alkaline phosphatase
D. obtain an endocrinology consultation
E. order pelvic ultrasonography

The National Health and Nutrition Examination Survey (NHANES) III and the National Health Examination Survey (NHES) indicate that the median age of menarche in United States girls is 12.43 years and has not changed over the past 3 decades. Certain ethnic differences have emerged, with non-Hispanic black girls having menses earlier than white girls and menses for Hispanic girls falling between these two groups. The interval between breast development (the first sign of puberty in females) and menstruation is 2.3+0.1 years,

but the range is 0.5 to 5.75 years. Most adolescents (62%) menstruate when they reach Sexual Maturity Rating (SMR) stage 4, with 26% in stage 3 and 11% in stage 5. Only 1% menstruate in stage 2. Menarche occurs approximately 3.3 years after the onset of the growth spurt and 1.1 years after the peak height velocity is attained. The percentage of body fat is critical; according to Frisch's theory, a minimum body fat value of 17% is required to initiate menses and a value of 22% is required to maintain regular cycles.

The girl described in the vignette has had a significant growth spurt, which indicates that she has entered puberty and is probably in SMR stage 2 or 3. If this is confirmed by clinical examination, no further evaluation is necessary and it is likely that the girl will begin menstruating in the next year or two. A mother's age of menstruation can be used as a guide for her daughters' menarche, but is not as useful as determination of her daughter's SMR. If a patient shows no sign of pubertal development by age 13.5 years or if there is no progression of puberty, endocrinologic consultation and performance of pelvic ultrasonography may be indicated. The bone age is a useful tool in patients who have delayed puberty because pubertal events correlate most closely with bone age and not chronologic age. Measuring serum alkaline phosphatase will not be of benefit in predicting menarche.

4. A 15-year-old girl presents for treatment of menstrual cramps. She had menarche 3 years ago, and over the last year, she has begun having pain on the first day of her cycle. She says that if she can get past the first day, the pain decreases and goes away in the next day or two. The herbal tea her mother was giving her no longer works.

Of the following, the MOST effective initial treatment for this girl's symptoms is
A. acetaminophen
B. calcium channel blocker
C. combined oral contraceptive
D. ibuprofen
E. omega-3 fatty acids

Dysmenorrhea or painful menstrual bleeding is the leading cause of recurrent, short-term school absenteeism and lost work time among adolescent girls. Primary dysmenorrhea refers to painful menses with normal pelvic anatomy and starts when menstrual cycles become ovulatory. A presumptive diagnosis can be based on a typical history of lower abdominal pain that begins shortly before or with the onset of menses and lasts 1 to 3 days with normal findings on physical examination. Potential associated symptoms include headaches, back pain, vomiting, and diarrhea.

The pathogenesis of primary dysmenorrhea is believed to be related to increased endometrial prostaglandin production, which causes myometrial contractility that, if excessive, leads to uterine ischemia and pain and the other associated symptoms. Elevated vasopressin concentrations also are observed in affected patients. Risk factors for primary dysmenorrheal include nulliparity, heavy menstrual flow, smoking, and poor mental health and social supports. If the history or examination findings are inconsistent with primary dysmenorrhea, further evaluation for secondary causes is necessary.

Initial therapy for dysmenorrhea includes drugs that inhibit the synthesis of prostaglandin through the prostaglandin synthetase system and antagonize their action at the cell receptor level. The most established medications are the nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen. They have been found to be significantly more effective for pain relief than placebo. Evidence is insufficient to determine which NSAID is the safest and most effective for the treatment of dysmenorrhea. However, clinical trials have shown that all NSAIDs are more effective than acetaminophen. These medications are available over the counter and, thus, should be the first line of treatment. Specific cyclooxygenase-2 inhibitors also may relieve dysmenorrhea symptoms.

In as many as 20% to 25% of patients, NSAIDs are not effective and alternate treatment such as combined hormonal contraceptives is indicated. Combined hormonal contraceptives act by suppressing ovulation and lessening the endometrial lining of the uterus. Therefore, both menstrual fluid volume and the amount of prostaglandins produced decreases, which effectively reduce dysmenorrhea by decreasing uterine motility and uterine cramping. Other hormonal contraceptive products have been used for treatment of dysmenorrhea, including depomedroxyprogesterone acetate and levonorgestrel intrauterine device. All hormonal methods of contraception are prescription medications and require a doctor's visit. This increases their cost in time and money. Therefore, they are recommended for use only if NSAIDs are not effective. Several medications that are effective in inducing uterine relaxation have been proposed as treatment for dysmenorrhea. For example, early uncontrolled trials of calcium channel blockers have shown promise but require further investigation.

Many consumers are seeking alternatives to conventional medicine, and research into the menstrual cycle suggests that nutritional intake and metabolism may play an important role in the cause and treatment of menstrual disorders. One small trial showed fish oil (omega-3 fatty acids) to be more effective than placebo for pain relief. However, evidence is not yet strong enough to recommend the use of any herbal and dietary therapies for the treatment of primary or secondary dysmenorrhea. Pelvic nerve interruption has been suggested for recalcitrant cases of dysmenorrhea, but this procedure is not recommended in the management, regardless of cause.

5. You are seeing a 15-year-old girl for her annual health supervision visit. Her menarche occurred at age 12 years, and she had normal monthly menses over the first 2 years. In the last year, however, her periods became progressively more irregular and stopped 4 months ago. Her mother notes that the girl has been very health-conscious since she entered puberty. She has gained no weight over the last 3 years and is on the cross-country team at school. On physical examination, her body mass index is 17 kg/m2, her heart rate is 55 beats/min, she has no acne or hirsutism, and she is at Sexual Maturity Rating 5 genital development. The remainder of the physical examination findings are normal.

Of the following, the MOST likely cause of this girl's amenorrhea is
A. ergogenic agents
B. exercise regimen
C. heart disease
D. physiologic anovulation
E. school stress

The American College of Sports Medicine coined the term "the female athlete triad" in 1992. It comprises three interrelated components: disordered eating, amenorrhea, and osteoporosis. The risk of the disorder is greatest among those participating in endurance sports. Athletes are distributed along a spectrum between health and disease, and those at the pathologic end may not exhibit all of the components simultaneously. The girl described in the vignette has amenorrhea that is related to her level of exercise and inadequate nutrition.

Nutrition issues underlie most of the pathophysiology of the female athlete triad. Energy availability is defined as dietary energy intake minus exercise energy expenditure. Exercise-induced amenorrhea can be an indicator of decreased energy availability that may be inadvertent, intentional, or psychopathological. Bone density loss results from the low estrogen environment and is concerning because 50% of adult skeletal mass is laid down during adolescence, with peak bone mass attained between ages 18 and 25 years.

The first aim of treatment for any triad component is to increase energy availability by increasing energy intake, reducing exercise energy expenditure, or both. Nutrition counseling and monitoring are sufficient for many athletes, but significantly disordered eating warrants more intensive intervention.

Education of athletes, parents, coaches, trainers, judges of competitions, and administrators is a priority for prevention and early intervention. Athletes should be assessed for the triad during preparticipation physical examination or the annual health screening examination and whenever an athlete presents with any of the triad's symptoms or signs. Sports administrators should consider rule changes to discourage unhealthy weight loss practices. Athletes who have eating disorders should be required to meet established weight criteria to continue exercising, and their training and competition may need to be modified.

Ergogenic aids are dietary supplements used to enhance athletic performance. The most commonly used are those that have supposed anabolic effects because they mimic the effects of steroids and are legal for use. Creatine is the most widely used such supplement taken by both professional and recreational athletes. It causes weight gain from muscle hypertrophy and fluid retention. It does not alter vital signs or cause menstrual changes. The girl described in the vignette has no symptoms referable to the cardiovascular system; her low heart rate likely is aresult of her inadequate nutrition and exercise. In the first 2 years following menarche, irregular menses may be the result of immaturity of the hypothalamic pituitary axis (physiologic anovulation). However, this girl's regular menses in the first 2 years make physiologic anovulation a less likely cause of the amenorrhea. Psychological stress in an adolescent may cause amenorrhea, but the history and examination findings of this girl are most consistent with amenorrhea resulting from exercise.

6. A 13-year-old girl presents with severe lower abdominal pain of 24 hours' duration. She states that the pain is sharp and constant and that she has had similar pain for several days approximately monthly over the past 4 months. She has no vomiting or diarrhea with the pain, but she is constipated frequently, having a bowel movement about every 3 to 4 days. She feels that her jeans are getting tighter around the waist, although she remains active, playing soccer daily. She has never had a menstrual period and denies ever being sexually active. On physical examination, she is afebrile, her heart rate is 85 beats/min, and her blood pressure is 110/70 mm Hg. Her weight is at the 60th percentile and her height at the 50th percentile for age. Her breasts and genitalia are at Sexual Maturity Rating 5. Abdominal examination reveals a firm and tender midline mass that is inferior to the umbilicus.

Of the following, the MOST likely diagnosis is
A. bladder obstruction
B. endometriosis
C. hematocolpos
D. megacolon
E. ovarian cyst

The adolescent described in the vignette has a clinical history and physical examination findings compatible with an imperforate hymen, which probably is the most common obstructive anomaly of the female reproductive tract. An adolescent patient who has an imperforate hymen may be asymptomatic or may have a history of cyclic abdominal pain that may occur for several years before the diagnosis is made. A bluish, bulging hymen may be seen on genital inspection, and a distended vagina may be palpated on rectoabdominal or abdominal examination. If the vagina becomes substantially enlarged with accumulated blood, the patient may experience back pain, pain with defecation that can result in constipation, nausea and vomiting, or difficulty in urinating.

Bladder outlet obstruction occurs rarely, and although it produces a suprapubic mass, it does not cause cyclic abdominal pain. Megacolon also is unlikely and does not cause cyclic pain, although colonic irritation may develop from the pressure produced by the mass. An ovarian cyst typically causes a right- or left-sided (not midline) mass, and endometriosis is an unlikely cause of a palpable mass, although it can cause cyclic and acyclic pain in adolescents.