Secondary Amenorrhea

Diane Bloomfield

Pediatr. Rev. 2006;27;113-114
DOI: 10.1542/pir.27-3-113

In Brief

Secondary Amenorrhea

Diane Bloomfield, MD
Children's Hospital at Montefiore
Bronx, NY

Author Disclosure

Dr Bloomfield did not disclose any financial relationships relevant to this In Brief.

Menstrual Cycle Abnormalities: Diagnosis and Management. Iglesias E, Coupey S. *Adolescent Medicine: State of the Art Reviews.* 1999;10: 255–273

Medical Concerns of the Female Athlete. *Pediatrics.* 2000;106:610–613

Eating Disorders in Adolescents and Young Adults. Kreipe R, Mou SM. *Obstet Gynecol Clin North Am.* 2000; 27:101–124

The Female Athlete Triad: Disordered Eating, Amenorrhea, Osteoporosis. Yeager KK, Agostini R, Nattiv A, Drinkwater B. *Med Sci Sports Exerc.* 1993;25:775–777

Secondary amenorrhea, the cessation of previously normal menstruation, should be considered in any female who has a gynecologic age of at least 24 months and has not menstruated for three or more consecutive cycles. The gynecologic age, the time in months since menarche, is the best indicator that a normal ovulatory pattern should have been established; regular monthly cycles are not reliably present until 2 years after menarche. The underlying causes of secondary amenorrhea can be understood from a review of the normal menstrual cycle.

The menstrual cycle is regulated by interplay within the hypothalamic-pituitary-ovarian axis. In normal ovulation, gonadotropin-releasing hormone (GnRH) starts the cycle by initiating the release of follicle-stimulating hormone (FSH) from the anterior pituitary gland. FSH promotes the maturation of an ovarian follicle, which is released at midcycle after a surge of luteinizing hormone (LH). The estrogen produced by the follicle supports the proliferative phase of the endometrium; the progesterone produced by the corpus luteum causes the endometrium to differentiate and stabilize. Approximately 14 days after ovulation, if the ovum is not fertilized, the rapid decline of the levels of estrogen and progesterone results in regression of the endometrium, with menstruation following.

Most commonly, secondary amenorrhea results from some disruption of the hypothalamic-pituitary-ovarian axis. The disrupting agent can range from a neoplasm, such as a craniopharyngioma or pituitary adenoma, to physical or emotional stress, which can induce a functional hypothalamic state in which reduced secretion of GnRH produces levels of LH and FSH that are too low to stimulate ovulation.

Female athletes are at risk for secondary amenorrhea from the loss of pulsatile LH release, directly related to reduced energy intake from dieting coupled with high energy expenditure from exercise. In addition, with reduced adipose tissue, athletes have lower levels of leptin, which normally helps trigger the secretion of GnRH. The triad of a disordered eating pattern, amenorrhea, and osteoporosis among female athletes is now well recognized, particularly among young women who compete in sports where leanness is emphasized, such as gymnastics, ballet dancing, figure skating, and long-distance running. The eating disorder, which can range from decreased food intake to vomiting and laxative abuse, most often is not severe enough to meet the criteria for anorexia nervosa. Still, it may have adverse consequences, leading, in time, to menstrual dysfunction and osteoporosis from hypoestrogenism. With appropriate weight gain, menses resume, and the loss of bone mineral density reverses.

Secondary amenorrhea can be an early signal of anorexia nervosa, occurring before weight loss becomes dramatic. Typically, menses ceases when body weight falls to 85% of the ideal for age and height, the result of hypothalamic dysfunction related to the weight loss itself and exacerbated by excessive exercise and stress. Interestingly, a patient who has moderate weight loss from a chronic illness such as inflammatory bowel disease is more likely to maintain menstruation than is an adolescent who has an eating disorder and has lost the same amount of weight. With a prevalence of 1 per 300 among 15- to 19-year-old adolescent women, anorexia nervosa is an important consideration in any patient who has secondary amenorrhea. Treatment centers on restoring and maintaining a normal body weight, at which time menses resumes. With longstanding anorexia and amenorrhea, hypoestrogenism and consequent osteopenia are risks. In this select group, hormone replacement therapy may be an option.

Although derangements of the hypothalamus and pituitary are the most common causes of secondary amenorrhea, most often related to emotional or physical stress, malfunction of the ovary also can interfere with normal menstruation. In functional ovarian hy-

perandrogenism, elevated ovarian androgen and an elevated LH/FSH ratio contribute to chronic anovulation. Also known as polycystic ovary syndrome, this common condition can be associated with hirsutism and evidence of hyperinsulinism, in particular with acanthosis nigricans. Pelvic ultrasonography may reveal polycystic ovaries, hence the syndrome's original name. Management involves oral contraceptives, which decrease GnRH production by negative feedback to the hypothalamus, ultimately reducing stimulation of the ovaries, resulting in a decrease in production of ovarian androgens. Hyperandrogenism also can result from late-onset congenital adrenal hyperplasia (21-hydroxylase deficiency) and from ovarian or adrenal tumors.

Failure of normal ovarian function, with consequent amenorrhea, also can result from an autoimmune process, often associated with thyroid dysfunction and diabetes mellitus. Patients who have ovarian failure have low levels of estradiol and elevated FSH levels from the absence of normal negative feedback. Amenorrhea from ovarian failure also can be seen in survivors of cancer as an effect of chemotherapy. The treatment of choice for ovarian failure is hormone replacement with oral contraceptives.

Stress-related conditions are the most common cause of secondary amenorrhea, followed in frequency among adolescent girls by pregnancy, and its possibility certainly needs to be considered. Finally, illicit drugs can cause secondary amenorrhea, and their use should be ruled out.

In Brief

Escherichia coli

Robin Goldman, MD
The Children's Hospital at Montefiore
Bronx, NY

Author Disclosure

Drs Goldman and Adam did not disclose any financial relationships relevant to this In Brief.

Diagnosis and Management of Food-borne Illnesses. *MMWR Morbid Mortal Wkly Rep.* 2001;50:(RR2):1–69

The Risk of the Hemolytic-Uremic Syndrome After Antibiotic Treatment of *Escherichia coli O157:H7 Infections.* Wong C, Jelacic S, Habeeb R, et al. *N Engl J Med.* 2000;342:1930–1936

An Outbreak of *Escherichia coli* O157:H7 Infections Among Visitors to a Dairy Farm. Crump J, Sulka A, Langer A, et al. *N Engl J Med.* 2002;347:555–560

***Escherichia coli* O157:H7.** Tarr P, Neill M. *Gastroenterol Clin North Am.* 2001;30:735–751

Escherichia coli are gram-negative bacilli in the *Enterobacteriaceae* family. Most of the many known strains of *E coli* are beneficial, colonizing the intestines of healthy humans and suppressing growth of pathogenic bacteria. However, at least five different pathotypes of diarrhea-producing *E coli* have been identified. Clinically, the disease caused by each pathotype is distinctive.

Enterotoxigenic *E coli* (ETEC) causes a self-limited illness, usually lasting fewer than 5 days. The organism colonizes the small intestine, where it releases an enterotoxin. Symptoms, usually of moderate severity, include nonbloody, watery diarrhea and abdominal cramps. On routine stool cultures, *E coli* organisms are read as "normal flora," so specific testing is required to diagnose ETEC. The most common cause of traveler's diarrhea, ETEC also is an increasingly recognized cause of food-borne illness in the United States. With the self-limited duration of its symptoms, ETEC infection generally does not require antibiotic therapy.

Enteroinvasive *E coli* (EIEC) infection often is associated with fever. The organism invades the colonic mucosa, where it induces a local inflammatory response. Diarrhea can be bloody, but is usually watery and without blood or mucus. The incidence of EIEC in developed countries is believed to be low, but occasional food-borne outbreaks have been identified.

Shiga toxin-producing *E coli* (STEC), formerly known as enterohemorrhagic *E coli* (EHEC) or verotoxin-producing *E coli*, is the only pathotype commonly responsible for diarrhea in children in the United States, and it can cause a hemorrhagic colitis with systemic complications. Both the hemolytic-uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) have been associated with STEC infection, with HUS more common among children and TTP among adults. In particular, *E coli* O157:H7 has emerged as the most virulent member of this pathotype, responsible both for outbreaks and for sporadic cases of diarrhea in North America. Typically, illness with *E coli* O157:H7 begins with 24 to 48 hours of nonbloody diarrhea that often, but not

always, is followed by frankly bloody stools. Severe cramping abdominal pain, nausea, and vomiting are typical. Fever, most often low-grade, is reported in only about one third of patients.

Annually, *E coli* O157:H7 infects about 75,000 people in the United States and causes about 60 deaths. Transmission is usually through food or water contaminated with animal or human feces, but person-to-person transmission also has been documented in households, nurseries, and hospitals. Healthy cattle are the primary recognized animal reservoir. Outbreaks have been linked to undercooked ground beef, unpasteurized milk and apple cider, raw vegetables, salad dressing, salami, yogurt, and water. Transmission also has been reported in persons swimming in a fecally contaminated lake as well as among visitors to dairy farms and petting zoos, where children have direct contact with the animals.

Infection with *E coli* O157:H7 is most common in the summer months. The incubation period for most *E coli* strains is from 10 hours to 6 days. For *E coli* O157:H7, it usually is 3 to 5 days, but can be as long as 8 days. The infectious dose of *E coli* O157:H7 is low; ground beef patties that have fewer than 700 organisms each have been associated with illness.

The illness caused by *E coli* O157:H7 typically is biphasic, beginning with localized intestinal disease, in which the pathogen attaches to the small-bowel mucosa, invades mucosal cells, and disrupts the microvillus brush border. The result is a secretory diarrhea. The second, systemic phase depends on production of a potent cytotoxin, the same toxin produced by *Shigella dysenteriae* type 1: shiga-toxin, also known as verocytotoxin or verotoxin. Absorbed into the systemic circulation, the toxin enhances thrombin formation, impairs fibrinolysis, and compromises blood flow to the kidneys, brain, and other organs, potentially resulting in HUS or TTP.

HUS is characterized by thrombocytopenia, hemolytic anemia, and nephropathy. Although it can have other causes, HUS among children most often results from infection with STEC, most commonly O157:H7. Approximately 10% of children younger than 10 years of age who are infected with *E coli* O157:H7 develop HUS, with a mortality rate of about 3% to 5%.

If *E coli* O157:H7 infection is suspected, specific testing must be requested. Clinical laboratories can screen for the organism by using MacConkey (SMAC) agar base with sorbitol. Most *E coli* strains rapidly ferment sorbitol, but O157 strains do not. Positive isolates should be forwarded to public health laboratories for confirmation and serotyping. Methods for definitive identification include DNA probes, polymerase chain reaction, and enzyme immunoassay. Shiga-toxin may be tested by using rapid diagnostic kits.

Treatment of *E coli* O157:H7 infection is supportive and involves correcting and maintaining fluid and electrolyte balance. Retrospective data suggest that antimicrobial agents may be harmful, possibly increasing the likelihood of HUS, perhaps by causing the release of shiga-toxin from injured bacteria in the intestine, making the toxin more available for absorption. The use of antimotility agents also is discouraged because they may delay clearance of the organism and lengthen the time of toxin absorption.

In view of the seriousness of human infection caused by *E coli* and the limited therapeutic options, preventing transmission is vital. Education and legislation should promote safe food preparation and food-handling practices. In child care centers, the most important prevention measure is supervised hand washing. Physicians can help prevent *E coli* O157:H7 infection by counseling families about the risk of eating undercooked ground beef and drinking unpasteurized milk and juice. Early reporting of cases to local health departments allows for earlier identification of the source of infection and more effective control of outbreaks.

Comment: An issue related to *E coli* that pediatricians commonly face is traveler's diarrhea: to offer prophylaxis or not? Several antibiotics, particularly ciprofloxacin and trimethoprim/sulfamethoxazole, are effective in preventing traveler's diarrhea, but evidence suggests that early treatment once symptoms have begun is a reasonable alternative to prophylaxis. Early treatment rapidly reduces the severity of diarrhea, and in an age when the emergence of drug-resistant pathogens has become a major problem throughout the world, widespread use of broad-spectrum antimicrobials as prophylaxis for travelers would surely lead to burgeoning resistance among coliforms. The best prophylaxis is good advice: stick to bottled beverages and bottled or boiled water, don't forget that ice is water, and avoid salads and fruits.

Henry M. Adam, MD
Editor, In Brief

Secondary Amenorrhea

Diane Bloomfield

Pediatr. Rev. 2006;27;113-114
DOI: 10.1542/pir.27-3-113