SUBSPECIALTY CONSULT

Dysmenorrhea and Irregular Uterine Bleeding

ysmenorrhea and menorrhagia beyond the norm often overlap in adolescents and can occur in up to 15% of these young women.

The normal time period from breast development (thelarche) and develop-

ment of pubic hair to menses in young girls is about 2 years. A longer time course is cause for investigation.

The maturation of the hypothalamic-pituitary-ovarian axis occurs over approximately 5 years. After initiation of menses (menarche), adolescents anovulatory cycles, i.e., no luteinizing hormone surge with subsequent lack of ovulation and dysfunctional es-

trogen effect on the uterine endometrial lining. This can present with irregular bleeding that can be very heavy when the endometrial lining sheds in an unsynchronized manner. If no other cause for this bleeding is established (for example, endocrine, anatomic, or underlying chronic disease), then it is considered dysfunctional uterine bleeding (DUB).

In the same time period of 5 years

from menarche, an estimated 15%-30% of young women will have primary dysmenorrhea strong enough to require pain medication, including nonsteroidal anti-inflammatory drugs (NSAIDs).

The vast majority of young adolescent

girls experience some pain with their periods, ranging from discomfort to pain requiring medication to being unable to go to school.

When the pain is severe, these patients either miss school or just make it through the school day, but their attention and performance suffer. These girls with significant pain need more assistance because their dysmenorrhea may not sub-

side for several years, and a referral to a subspecialist is warranted.

In terms of differential diagnosis, menstrual pain (dysmenorrhea) is a crampy, focal phenomenon in the mid-lower quadrant, sometimes with radiation to the back and the lower extremities. It starts with the onset of menses. If the pain precedes menses, it may be endometriosis and not primary dysmenorrhea, although there is an overlap in the pain symptoms between these two entities. A nonleading question to ask is whether the patient experiences pain before, during, or after her cycle.

A gastrointestinal etiology is more likely if the pain is nonfocal and present in all four quadrants. Ruling out other GI etiologies, particularly constipation, is important. A trial of Miralax over 2-3 weeks with a cessation in the pain easily confirms constipation as the underlying cause. Constipation is very common in children and adolescents, and the pain is not related to the menstrual cycle.

Dysmenorrhea is a clinical diagnosis. Laboratory tests for this condition are not needed. Instead, a good history, detailed description of the pain, and ultrasound examination (transabdominal, not transvaginal) aid the differential diagnosis. Ultrasound is reassuring, as it can show normal uterine development

and no ovarian masses, including no benign childhood ovarian tumors. Rarely is a pelvic examination necessary.

Pediatricians are instrumental in terms of edu-

cating patients, encouraging these patients to keep a detailed menstrual and pain diary, and advocating appropriate use of NSAIDs. However, if the diagnosis and management of teenagers with dysmenorrhea are outside your comfort zone, or your focus is primarily on younger children, you can refer the patient to a pediatric and adolescent gynecologist or other adolescent medicine specialist.

One problem for these patients is the use of Tylenol, which does not work on the elevated prostaglandins in primary dysmenorrhea. Instead, recommend an NSAID such as ibuprofen (Motrin, Advil), naproxen (Naprosyn), or mefenamic acid (Ponstel).

If pain relief is inadequate, switch classes of NSAIDs instead of switching between drugs in the same class.

Birth control pills are another option for controlling painful periods. For most girls with menses painful enough to impair their activities of daily living, birth control pills are a huge benefit. Oral contraceptives for 1-2 years for irregular bleeding and dysmenorrhea can make a big difference, and then you can try a trial period without them. Prescription of birth control pills requires a lot of education, particularly because these young patients need to be compliant. Create a routine for them-such as suggesting their pills be stored in a secure location with their toothbrush.

Parents also need to be vested in this approach, and some will be resistant. I recommend that you discuss birth control pills as a strategy to control pain and bleeding when the parents and the patient are both present. Educate parents that birth control pills will not give their daughters breast cancer or cause them to become sexually active. Any generic monophasic oral contraceptive with 30 mcg of estradiol can be used.

If you add birth control pills to NSAIDs, 95% of patients experience no pain or bearable pain. It can take up to 6 months for maximum relief, however, and these teenagers need to keep a menstrual and pain diary to track and appreciate the improvements over time.

Heating pads can be a comforting, nonpharmacologic strategy for managing dysmenorrhea. Some girls who use them report taking fewer NSAIDs. There also is some literature on the benefits of acupuncture, but it is not always practical in the United States.

DUB is a diagnosis of exclusion. In your differential diagnosis, rule out thyroid dysfunction, prolactinoma (a rare

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brain tumor), or any underlying chronic diseases (such as lupus) that affect the menstrual cycle. If you suspect anatomic abnormalities, a transabdominal ultra-

sound examination is indicated. You also have to consider polycystic ovarian syndrome (PCOS), because teenagers with this syndrome can present with irregular

Laboratory tests for DUB are thyroid function, prolactin, and markers for PCOS. These assays include free and total testosterone, sex hormone-binding globulin, and androstenedione.

Most pediatricians know this, but if the first menses (menarche) is very heavy, you have to think of a bleeding disorder. This is an important diagnostic sign that additional work-up is warranted, and early intervention may be possible. If there is a bleeding disorder, early diagnosis could mean a lesser chance of hemorrhage during childbirth. Awareness among pediatricians is important because young girls rarely see gynecologists.

Classic DUB is related to menstrual cycle irregularities. There is a cohort of eggs recruited in the first half of the cycle (follicular phase). One follicle emerges that will rupture and release the egg at midcycle after luteinizing hormone levels spike in the body. If this sequence does not occur, the menstrual cycle is affected. The endometrial lining has proliferated under the effect of estrogen, and unsynchronized shedding with irregular bleeding occurs.

Again, you can take control of the menstrual cycle with birth control pills.

DR. MAMA is a pediatric and adolescent ob.gyn. at Cooper University Hospital in Camden, N.J. He said he had no relevant financial disclosures.



ophthalmic solution) 0.2%

Pataday

INDICATIONS AND USAGE
PATADAY™ solution is indicated for the treatment of ocular itching associated with allergic conjunctivitis.

CONTRAINDICATIONS

Hypersensitivity to any components of this product.

WARNINGS

For topical ocular use only. Not for injection or oral use.

Information for Patients

As with any eye drop, to prevent contaminating the dropper tip and solution, care should be taken not to touch the eyelids or surrounding areas with the dropper tip of the bottle. Keep bottle tightly closed when not in use. Patients should be advised not to wear a contact lens if their

eye is red. PATADAY™ (olopatadine hydrochloride ophthalmic solution) 0.2% should not be used to treat contact lens related irritation. The preservative in PATADAY™ solution, benzalkonium chloride, may be absorbed by soft contact lenses. Patients who wear soft contact lenses and whose eves are not red. should be instructed to wait at least ten minutes after instilling PATADAY™ (olopatadine hydrochloride ophthalmic solution) 0.2% before they insert their contact lenses.

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 Carcinogenesis, Mutagenesis, Impairment of Fertility
 Olopatadine administered orally was not carcinogenic in mice and
 rats in doses up to 500 mg/kg/day and 200 mg/kg/day, respectively.
 Based on a 40 μ L drop size and a 50 kg person, these doses were
 approximately 150,000 and 50,000 times higher than the maximum
 recommended ocular human dose (MROHD). No mutagenic potential
 was observed when olopatadine was tested in an *in vitro* bacterial
 reverse mutation (Ames) test, an *in vitro* mammalian chromosome
 aberration assay or an in vivo mouse micronucleus test. Olopatadine
 administered to male and female rats at oral doses of approximately
 100,000 times MROHD level resulted in a slight decrease in the fertility
 index and reduced implantation rate; no effects on reproductive function
 were observed at doses of approximately 15,000 times the MROHD
 level.

Pregnancy:
Teratogenic effects: Pregnancy Category C
Olopatadine was found not to be teratogenic in rats and rabbits.
However, rats treated at 600 mg/kg/day, or 150,000 times the MROHD and rabbits treated at 400 mg/kg/day, or approximately 100,000 times the MROHD, during organogenesis showed a decrease in live fetuses. In addition, rats treated with 600 mg/kg/day of olopatadine during organogenesis showed a decrease in fetal weight. Further, rats treated with 600 mg/kg/day of olopatadine during late gestation through the lactation period showed a decrease in neonatal survival and body weight.

weight.
There are, however, no adequate and well-controlled studies in pregnant women. Because animal studies are not always prodiction of the studies are not always prodiction. women. Because animal studies are not always predictive of human responses, this drug should be used in pregnant women only if the potential benefit to the mother justifies the potential risk to the embryo

Nursing Mothers:

Olopatadine has been identified in the milk of nursing rats following oral administration. It is not known whether topical ocular administration could result in sufficient systemic absorption to produce detectable quantities in the human breast milk. Nevertheless, caution should be exercised when PATADAY™ (olopatadine hydrochloride ophthalmic solution) 0.2% is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in pediatric patients below the age of 3 years have not been established.

No overall differences in safety and effectiveness have been observed between elderly and younger patients.

ADVERSE REACTIONS

purpose near times, myptoms similar to cold syndrome and pharyngitis were reported at an cidence of approximately 10%.

The following adverse experiences have been reported in 5% or less

The following adverse experiences have been reported in 5% or less of patients:
Ocular: blurred vision, burning or stinging, conjunctivitis, dry eye, foreign body sensation, hyperemia, hypersensitivity, keratitis, lid edema, pain and ocular pruritus.

Non-ocular asthenia, back pain, flu syndrome, headache, increased cough, infection, nausea, rhinitis, sinusitis and taste perversion.

Some of these events were similar to the underlying disease being studied.

DOSAGE AND ADMINISTRATION

The recommended dose is one drop in each affected eye once a day.

HOW SUPPLIED

PATADAY™ (olopatadine hydrochloride ophthalmic solution) 0.2% is supplied in a white, oval, low density polyethylene DROP-TAINER® dispenser with a natural low density polyethylene dispensing plug and a white polypropylene cap. Tamper evidence is provided with a shrink band around the closure and neck area of the package.

2.5 mL fill in 4 mL oval bottle

Storage: Store at 2°C to 25°C (36°F to 77°F) U.S. Patents Nos. 4,871,865; 4,923,892; 5,116,863; 5,641,805; 6,995,186

- 1. Abelson MB. Gomes PJ. Pasquine T. et al. Efficacy of olopatadine ophthalmic solution 0.2% in reducing signs and symptoms of allergic conjunctivitis. *Allergy Asthma Proc.* 2007;28:427-433.

 2. PATADAY" Solution Package Insert.

 3. Vogelson CT, Abelson MB, Pasquine T, et al. Preclinical and clinical
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 Wolters Kluwer Health, Source® Pharmaceutical Audit Suite. August 2009-September 2010.

 Wolters Kluwer Health, Source® Pharmaceutical Audit Suite. September 2008-August 2009.



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