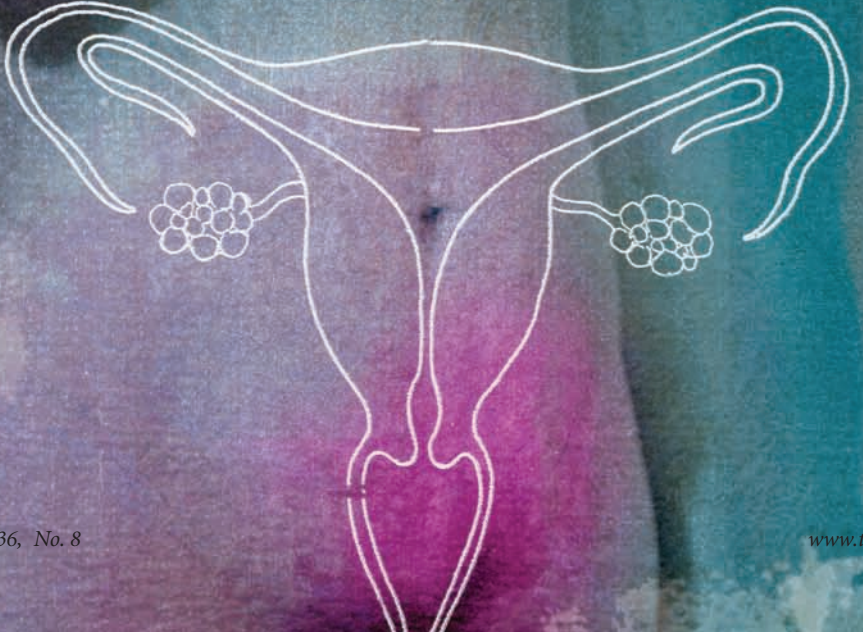
Treatment options for Dysfunctional uterine bleeding



CE 2.5 CONTACT HOURS

Abstract: The diagnosis and treatment of dysfunctional uterine bleeding can be a long emotional journey for the patient and a difficult challenge for the provider. This article provides NPs with a practical overview of the process from chief complaint to follow-up care.

By C. Michelle Thomas, MSN, FNP-C

It is estimated that 5% of women between the ages 30 and 49 will seek treatment each year for dysfunctional uterine bleeding (DUB); 30% of all women report having experienced DUB at some time.[1] Although DUB is a very common women's health issue, it is a diagnosis of exclusion, and can be frustrating for practitioners who are trying to identify the condition and for the patient who is experiencing DUB.

The evaluation and management of any abnormal uterine bleeding is a complex process involving many decisions being made concurrently. Currently, there are no guidelines for comprehensive evaluation and management of DUB, and most existing guidelines focus on narrow and specific etiology and age groups. A recent medline search found 24 articles with treatment algorithms for abnormal uterine bleeding, of these only one was evidence-based and it was specific only to menorrhagia.[2]

In addition to the difficulties with the diagnosis and treatment of the physical condition, the psychosocial implications for these patients can also be overwhelming. NPs are in a unique position to help patients manage both physical and emotional issues of DUB.

Epidemiology

DUB is defined as "abnormal uterine bleeding that is not associated with a physical lesion, inflammation or pregnancy."[3] Bleeding can be excessively heavy or light and prolonged; it can be frequent or random, and is typically unpredictable. Ninety percent of DUB is anovulatory.[1,3]

As the most common cause of abnormal uterine bleeding, it affects both ends of the reproductive spectrum (that is, teens and perimenopausal women).[1] Teens typically experience DUB during the first 2 years after menarche begins, when their hypothalamic-pituitary-adrenal axis (HPA axis) is immature. Abnormal uterine bleeding affects up to 50% of perimenopausal women, and DUB in these women is most likely caused by a decline in ovarian function.[1] It is also of note that 20% of women diagnosed with endometriosis have anovulatory DUB, although the mechanism of this phenomenon is not currently known.[1]

Pathophysiology

There are three phases that constitute the menstrual cycle: (1) follicular/proliferative, (2) luteal/secretory, and (3) menstrual (if there is no fertilization and subsequent implantation). In a healthy menstrual cycle, the hypothalamus secretes gonadotropin-releasing hormone (GnRH) in a pulsatile manner (see *Hypothalamic-pituitary feedback control of estrogen and progesterone levels in the female*). In turn the pituitary gland responds to GnRH by releasing luteinizing hormone (LH) and follicle-stimulating hormone (FSH). In the follicular phase of the menstrual cycle, LH acts primarily on the theca cells of the ovary to increase the production of androgenic precursors. Concurrently, FSH acts on the granulosa cells to promote conversion of the androgens into estrogens, particularly estradiol, which facilitates follicular development.

During the follicular phase, increasing levels of estradiol lead to an LH surge, which stimulates ovulation. The combination of the LH surge, the elevated levels of estradiol, and an increase in the circulating progesterone level trigger the midcycle surge of FSH. Estrogen levels peak during the surge and then begin to decline as progesterone levels begin to increase. During the luteal phase, LH and FSH levels decrease. The ruptured follicle closes after releasing the ovum and forms a corpus luteum, which produces progesterone. Progesterone and estrogen cause the lining of the uterus to mature and become plump, in order to receive a fertilized ovum. If the ovum is not fertilized, the corpus luteum degenerates and no longer produces progesterone. Once the estrogen level decreases, the top layers of the uterine lining break down and are shed as menstrual flow.

Approximately 90% of cases of DUB are secondary to anovulation.[1,3] Without ovulation, the corpus luteum cannot form and subsequently there is inadequate progesterone

Illustration by Darren Hopes/Getty images ©

Key words: Abnormal uterine bleeding, menometrorrhagia, menstrual cycle, treatment of dysfunctional uterine bleeding

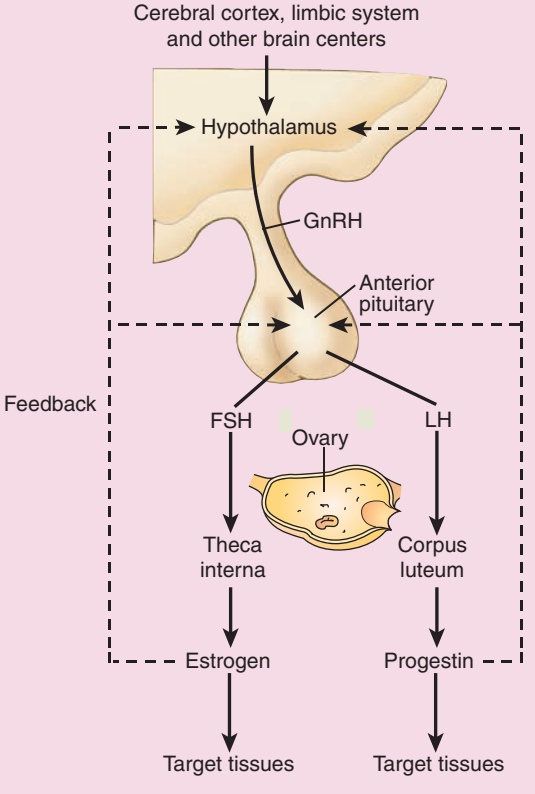
secretion. The resulting unopposed estrogen allows the endometrium to proliferate unimpeded. This overgrowth of the endometrial lining finally outgrows its blood supply and degenerates resulting in asynchronous breakdown of the lining at different levels and heavier than usual bleeding.

Some potential causes of anovulatory uterine bleeding include excessive exercise, emotional stress, eating disorders, polycystic ovarian syndrome (PCOS), obesity, and thyroid disease.

Reaching the diagnosis

Reaching a diagnosis means ruling out other possible pathologies, pharmacologic causes, and systemic disease, as well as establishing the irregularities in the patient's cycle. The typical menstrual cycle is 24 to 35 days in length with a flow lasting 2 to 7 days.[4] Blood loss from the average menstrual cycle is 35 to 50 mL, and menstrual blood differs from bleeding from an injury in that it does not clot unless it is very heavy (see *Assessing menstrual flow*).[1] The average patient changes pads every 3 hours and uses less than 21 for a menses.[4]

Hypothalamic-pituitary feedback control of estrogen and progesterone levels in the female



Source: Porth CM, Matfin, G. *Pathophysiology Concepts of Altered Health States*. 8th ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2009:1119.

Initially, the NP should rule out pregnancy; following that confirmation, any cervical or uterine abnormality should be explored. Cervical cancer, infection, trauma, or polyps can cause abnormal vaginal bleeding. Uterine causes can include leiomyomas, infection, polyps, endometrial hyperplasia, endometrial intraepithelial neoplasia, carcinoma, or the presence of a foreign body.

Medications that can cause increased risk for bleeding and therefore abnormal vaginal bleeding include the following: anticoagulants, selective serotonin reuptake inhibitors, antipsychotics, corticosteroids, hormonal supplements, phenytoin, or the herbal supplements soy and ginseng. The practitioner should compile a complete medication list, including over-the-counter vitamins or supplements.

Systemic diseases, such as those pertaining to the thyroid, adrenal glands, liver, kidney, or hematologic coagulopathies, should also be considered, as they can cause heavy uterine bleeding through: (1) inappropriate hormone production, (2) interference with pathways of the HPA axis, or (3) disruption of the hematologic coagulation pathway. For example, thyroid dysfunction can result in thyroid hormone imbalance resulting in HPA axis disruption and subsequently heavy bleeding (hypothyroidism) or amenorrhea (hyperthyroidism).

Over the past decade, there has been debate whether tubal ligation is a cause of abnormally heavy uterine bleeding. Although a case-control study showed that tubal sterilization did not cause menstrual irregularities, it still remains a matter of debate.[4]

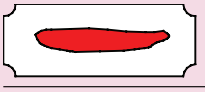
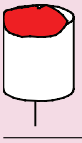
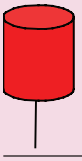
Case study

Camille, a 47-year-old woman who has had two pregnancies that resulted in two full-term live births (G2P2002) and is sexually active, presents with heavy vaginal bleeding, and claims she has been experiencing it for 6 weeks. She is fatigued, miserable, and frustrated. She laments: "Why is my body betraying me, I've been regular all my life?"

Camille is using barrier contraception, and her beta subunit human chorionic gonadotropin (beta-HCG) level is zero, confirming that she is not pregnant. It is established that at 6 weeks, Camille's bleeding far exceeds the typical length; however, "heavy flow" needs to be quantified. Camille claims she is using a "super absorbent" tampon with an "overnight" super absorbent pad, changing it 8 times/day, with a high level of saturation. When asked to compare any clots to the size of coins, she replies "the size of a dime."

After quantifying Camille's blood loss, she is diagnosed with menometrorrhagia, which is uterine bleeding that is excessive or prolonged occurring at irregular intervals. Camille now needs to be examined for any blood dyscrasia (that is, von Willebrand disease, idiopathic thrombocytopenic purpura, or leukemia).[5] Blood testing should include

Assessing menstrual flow

Date of day 1 of period / /	Day 1	Day 2	Day 3	Day 4	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Absorbency of pad (circle one)										
L= Liner	L	L	L	L	L	L	L	L	L	L
M=Maxi	M	M	M	M	M	M	M	M	M	M
O=Overnight	O	O	O	O	O	O	O	O	O	O
Saturation (check one) 										
										
										
Absorbency of tampon (circle one)										
J=Junior	J	J	J	J	J	J	J	J	J	J
R=Regular	R	R	R	R	R	R	R	R	R	R
S=Super	S	S	S	S	S	S	S	S	S	S
Saturation (check one) 										
										
										
Clots Number and coin size										

complete blood cell count, thyroid-stimulating hormone (TSH), and prolactin.

Testing reveals mild anemia (a hemoglobin level of 9.5 g/dL), which, except for her claims of "feeling a little tired," means she is otherwise asymptomatic; however, any menses with enough blood loss to cause anemia should be considered abnormal. Treatment with oral iron is initiated in the form of ferrous sulfate.

Camille is scheduled for a Pap smear, pelvic exam, screening for sexually transmitted infections (STIs), endometrial biopsy (EMB), and pelvic and transvaginal ultrasound. The American Congress of Obstetricians and Gynecologists (ACOG) recommend endometrial sampling in women 35 years and older presenting with any abnormal uterine bleeding.[3] STI screening is also required as gonorrhea and chlamydia can present with excessive bleeding attributed to copious discharge mixed with blood.

Her pelvic exam reveals a nontender uterus that is not markedly enlarged and a parous healthy appearing cervix and a subsequent normal Pap smear. The pelvic and vaginal ultrasound also reveals no abnormalities. Her endometrium measures 9 mm—endometrial thickness varies in menstruating

women from 4 mm in the early proliferative phase to 13 mm in the late secretory phase.[5]

General notes on diagnostic workup

If a patient exhibits typical signs and symptoms of PCOS, such as hirsutism, obesity, metabolic syndrome, acanthosis nigricans, and acne, the following additional tests would be needed: insulin level, LH, FSH, LH/FSH ratio, 17 alpha-hydroxyprogesterone, estradiol, testosterone (free and total), and dehydroepiandrosterone sulfate (DHEAS).

If abnormal thyroid findings or hyperprolactinemia (suggestive of pituitary prolactinoma, a noncancerous pituitary tumor that produces prolactin) had been detected, further workup would be warranted and consultation with or referral to an endocrinologist would be pursued as indicated. Hyperprolactinemia causes menorrhagia by disrupting GnRH secretion leading to decreased FSH and LH levels, and it can be detected by magnetic resonance imaging (MRI).[6] If the tumor is large enough to damage the optic nerve, surgical intervention may be necessary.

There are two additional exams that can be performed: the hysteroscopy and the saline infusion sonohysterography. The hysteroscopy provides excellent visualization of the endometrial cavity, but the saline infusion sonogram provides a better visualization of the myometrium or ovaries.[8] The hysteroscopy is useful because interventions such as polypectomy can be performed at the time of exam. The in-office hysteroscopy has become the procedure of choice over the same-day surgical procedure of dilation and curettage (D&C).[8] It has been suggested the saline infusion sonohysterography is a more sensitive test than the hysteroscopy.[3,9] This procedure involves infusing a small amount of sterile saline into the uterus via a small catheter, which distends the collapsed uterine walls permitting visualization of any cavity abnormalities (such as polyps or leiomyomas) with less invasive ultrasonography.

Goal of treatment

The goal in the treatment of DUB is to halt the acute bleeding episode and prevent recurrence. If the patient wishes to become pregnant, the secondary goal would be to restore ovulation. Timely and correct diagnosis is critical as improper diagnosis can lead to incorrect medical management, unnecessary surgery, and endometrial hyperplasia or carcinoma (up to 2% of women with inappropriately managed anovulatory bleeding eventually develop endometrial adenocarcinoma).[7] Arriving at a diagnosis may require several diagnostic tests that provide no definitive answers, and the NP needs to reassure the patient that every avenue is being explored to find the root of her medical condition. This reassurance cannot be understated, as a large component in the management of DUB is psychological and ample reassurance is a vital therapeutic tool.

If a hormone deficiency or systemic illness is detected in the patient's workup, then the appropriate treatment for that ailment would be administered. This may require collaboration with or referral to an endocrinologist or hematologist. If a prolactinoma is present that does not require surgery, treatment is oral bromocriptine 1.25 to 2.5 mg by mouth initially, increased gradually over 2 to 7 days until a therapeutic response is achieved. The drug is given in divided doses and should be taken with food to decrease gastrointestinal upset.

If neither of those apply, hormone therapy is the first-line treatment for DUB. Combination oral contraceptives (COCs) suppress endometrial development by reducing LH and FSH secretion and by reestablishing predictable bleeding patterns and resulting in a lighter flow. The NP should evaluate the patient for the benefits and risk associated with COC use. Patients taking COCs should be advised not to smoke because smoking increases the risk of adverse cardiovascular events especially in women over age 35.[1] COCs are contraindicated in patients with arteriothromboembolic disease (myocardial infarction, stroke), history of or active deep vein thrombosis (DVT) or pulmonary embolus (PE), untreated hypertension, diabetes mellitus with vascular complications, breast cancer, estrogen-dependent neoplasia, undiagnosed abnormal genital bleeding, and active liver disease.[1]

Conjugated estrogen (Premarin) alone can be administered in high doses in cases of hemorrhagic uterine bleeding.[8] Severe cases may require inpatient treatment with I.V. estrogen.[8] This treatment is effective in rapid cessation of hemorrhage because it exerts a vasospastic action on capillary bleeding by affecting the level of fibrinogen, factor IV, and factor X in blood. It also acts on platelet aggregation and capillary permeability. Estrogen induces formation of progesterone receptors, making subsequent treatment with progestins more effective.[8] Estrogen therapy should only be used to control an acute bleeding situation as it does not treat the underlying cause.

Unopposed estrogen therapy also has risks, including DVT, PE, stroke, and endometrial hyperplasia/carcinoma. Progestin should be added immediately after the hemorrhage is controlled to prevent a later bleeding episode. If the COC is contraindicated, cyclic oral micronized progestin daily for 10 to 12 days per month promotes predictable uterine withdrawal bleeding.[1] Although there are little data that suggest that progestin-only therapy is associated with increased risk of thrombotic events, caution should be exercised when considering its use.

For women unable to tolerate systemic hormones, the levonorgestrel-releasing intrauterine device (IUD) (Mirena) is an alternative; the drug received FDA-approval

in 2009 for women with heavy menstrual bleeding who choose intrauterine contraception. This method controls the endometrium with low dose (20 mcg/day) local release of progestin.[6] Studies report an 80% decrease in menstrual blood loss after 3 months and 90% decrease after 6 months of the insertion of this IUD. In 20% of study participants, menstrual bleeding had ceased altogether at 6 months.[10]

In November 2009, the FDA approved tranexamic acid (Lysteda) as the first nonhormonal drug to treat heavy menstrual bleeding.[6] It slows bleeding quickly (within 2 to 3 hours) because it helps stabilize and preserve the fibrin matrix by moderating plasmin activity. It is taken only a few days a month during menses, and is an option for patients who may wish to become pregnant in the near future. Tranexamic acid is contraindicated in women who have a history of or have active thromboembolic disease. Historically, androgen medications such as danocrine have been used to treat anovulatory bleeding; however, they have been known to cause irreversible masculinization of patients and are seldom used today.

Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit blood prostacyclin formation, and can effectively decrease uterine blood flow, and there is currently only one NSAID marketed that has this indication from the FDA. Although NSAIDs have been shown to treat menorrhagia in ovulatory cycles, they generally are not effective for the management of anovulatory DUB.[8]

Another approach includes the short-term (up to 6 months) use of a GnRH agonist (leuprolide acetate). This medication suppresses gonadotropin, induces a medical castration, and breaks the ongoing cycle of abnormal bleeding in many anovulatory patients.[10] Prolonged therapy with GnRH agonists, however, is associated with osteoporosis and other postmenopausal adverse reactions. Its use is often limited in duration and "add back" therapy with a form of low-dose estrogen and progestins hormonal replacement is given if therapy must extend beyond 6 months.[10] Because of the expense of this drug, it is generally not a first-line approach, but can be used to achieve short-term relief from a bleeding problem or as preparation for surgical intervention.

When medical intervention fails

When medical treatment is contraindicated or it fails to control and prevent recurrent DUB, a referral to a gynecologic surgeon is indicated. Surgical options include D&C, endometrial ablation, and hysterectomy.

D&C, used to control sudden, heavy vaginal bleeding, is the quickest way to stop uterine bleeding and is both a diagnostic and a therapeutic procedure. Without subsequent hormone therapy, however, heavy bleeding usually returns.

Endometrial ablation is a procedure that destroys the endometrium. It is an option for patients seeking to avoid hysterectomy or who are not candidates for major surgery.[8] Techniques used for ablation include laser, electrosurgery excision procedure, freezing, heated fluid infusion, or thermal balloon ablation. Most women will have reduced menstrual flow following endometrial ablation, and up to half will stop having periods. Younger women are less likely than older women to respond to endometrial ablation. After an endometrial ablation, younger women are more likely to continue to have periods and need a repeat procedure.[11] Recent scientific evidence supports that up to one quarter of patients treated with endometrial ablation require repeat ablation or subsequent hysterectomy to stop DUB.[11] Hysterectomy should be considered a last resort for DUB when blood loss impedes health.

Research

Recent research is focused on antiprogestins. This is a likely treatment option because when administered during the follicular phase it postpones both the estrogen rise and the LH surge, and delays endometrial maturation.[12] On rare occasions, antiprogestins have been associated with endometrial hyperplasia, which is presumed to be a function of the unopposed estrogen activity (although this has not proven true in low doses).[12] Animal research is also ongoing with progestin antagonist releasing IUDs.[13]

Case study revisited

Reviewing Camille's history and considering her age and her lack of desire for additional pregnancies, the progestin-releasing IUD is the most appropriate choice of treatment.

After 3 months of treatment, Camille reported a significant decrease in her menstrual flow (one regular absorbency tampon changed every 4 hours that is not saturated on her heaviest day and no clotting). At this time, her hemoglobin count has returned to normal range and she states she feels less tired.

At 6 months, she reported that her menses had ceased and she now feels "great." Camille has resumed her active lifestyle that she had feared was a thing of the past for her.

Implications for practice

NPs in family practice, women's health, and even pediatrics may encounter DUB, and they can perform the majority of the workup including office hysteroscopy with specialized training (patients with an endocrine or hematologic disorder should be referred to an endocrinologist for the initiation of treatment, but may be referred back to the NP for maintenance). If medical therapy fails, a gynecologic surgeon should be consulted.

DUB should be suspected if a patient presents with irregular, episodic bleeding not preceded by moliminal symptoms in spite of a normal pelvic exam. Carefully consider all

possible diagnoses before reaching the conclusion that DUB is correct. Tailor the treatment plan to the patient based on age, hemodynamic stability, severity of bleeding, additional symptoms, and desire for future fertility. Remember that after initial treatment resolves, the patient needs to be educated regarding the probable need for chronic therapy and meticulous journaling of a menstrual calendar.

It is also apparent that the psychosocial implications for these patients can be overwhelming. Many who experience DUB may suffer in silence because they believe it is a "normal" part of aging. They may have a poor quality of life due to fear of social embarrassment related to unpredictable or heavy bleeding soiling their clothing. Some may restrict outings, travel, or activities once enjoyed to remain near restroom facilities. They may go through emotions similar to those of a person adapting to a chronic ailment. NPs should be aware of local support or counseling groups and educate patients who may benefit from these resources to seek additional emotional and social support.

REFERENCES

1. Estephan A, Sinert RH. Dysfunctional uterine bleeding. *eMedicine*. 2010. http://emedicine.medscape.com/article/795587-overview.
2. Guido RS, Stovall DW. Endometrial sampling procedures. *UpToDate* [online serial]. Waltham, MA: UpToDate; 2008.
3. ACOG Committee on Practice Bulletins—Gynecology. American College of Obstetricians and Gynecologists. ACOG practice bulletin: management of anovulatory bleeding. *Int J Gynaecol Obstet*. 2001;72(3):263-271.
4. Shobeiri MJ, Atashkhoii S. The risk of menstrual abnormalities after tubal sterilization: a case control study. *BMC Womens Health*. 2005;5(1):5.
5. Porter MRS, ed. *Merck Manual (Online Medical Library)*. Merck Sharp & Dohme Corp.; 2009.
6. Maness DL, Reddy A, Harraway-Smith CL, Mitchell G, Givens V. How best to manage dysfunctional uterine bleeding. *J Fam Pract*. 2010;59(8):449-458.
7. Apgar BS, Kaufman AH, George-Nwogu U, Kittendorf A. Treatment of menorrhagia. *Am Fam Physician*. 2007;75(12):1813-1819.
8. Hill DA. Abnormal uterine bleeding: avoid the rush to hysterectomy. *J Fam Pract*. 2009;58(3):136-142.
9. Mathew M, Gowri V, Rizvi SG. Saline infusion sonohysterography—an effective tool for evaluation of the endometrial cavity in women with abnormal uterine bleeding. *Acta Obstet Gynecol Scand*. 2010;89(1):140-142.
10. Behera MA, Price TM. Dysfunctional uterine bleeding. *eMedicine*. 2010. http://emedicine.medscape.com/article/257007-overview.
11. Lobo RA. Abnormal uterine bleeding: ovulatory and anovulatory dysfunctional uterine bleeding, management of acute and chronic excessive bleeding. In: *Comprehensive Gynecology*. Vol. 5th. Philadelphia, PA: Mosby Elsevier; 2007:915-931.
12. Ely JW, Kennedy CM, Clark EC, Bowdler NC. Abnormal uterine bleeding: a management algorithm. *J Am Board Fam Med*. 2006;19(6):590-602.
13. Chabbert-Buffet N, Meduri G, Bouchard P, Spitz IM. Selective progesterone receptor modulators and progesterone antagonists: mechanisms of action and clinical applications. *Hum Reprod Update*. 2005;11(3):293-307.

C. Michelle Thomas is a Family NP at Cigna Medical Group in Gilbert, Ariz.

The author has disclosed that she has no financial relationship related to this article.

DOI-10.1097/01.NPR.0000399716.79607.39