

## Learning Objectives

After reading this *CME Bulletin*, you should be able to:

- Distinguish between dysfunctional uterine bleeding and other types of abnormal uterine bleeding.
- Identify the most appropriate diagnostic tools to rule out other possible causes of abnormal uterine bleeding.
- Prescribe appropriate treatment for dysfunctional uterine bleeding based on each patient's individual needs.

## Diagnosis and Management of Dysfunctional Uterine Bleeding

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### Introduction

Abnormal uterine bleeding (AUB) affects up to one-third of women of reproductive age,<sup>1</sup> and can be physically and socially debilitating. AUB may be associated with symptoms such as fatigue and pain, and it may significantly affect a woman's quality of life, limiting her normal daily activities and diminishing her sex life.

AUB is defined as any bleeding that differs in regularity, frequency, duration or volume from a patient's usual menstrual flow.<sup>1</sup> Although it is a common complaint in the family medicine office setting, AUB can sometimes be a deceptively challenging condition. The etiology of AUB encompasses a wide range of disorders, including anovulation, pregnancy-related conditions, trauma, anatomic abnormalities of the genital tract, infection, endocrinologic disorders, malignancies and systemic illness.<sup>2</sup>

Dysfunctional uterine bleeding (DUB), which is associated with functional abnormalities of the hypothalamic-pituitary axis, is the diagnosis usually given when no clear systemic, anatomic or infectious etiology is identified.<sup>3</sup> DUB, which accounts for the vast majority of patients who report abnormal menstrual bleeding,<sup>4</sup> is the focus of this *Bulletin*. Systemic, anatomic and infectious causes of AUB are beyond the scope of this *Bulletin*.

### Pathophysiology

DUB is a diagnosis of exclusion that can only be established once structural and pregnancy-related causes have been ruled out.<sup>3,5,6</sup> Anovulatory DUB is usually characterized by bleeding that is irregular in timing and quantity.<sup>2</sup> Rarely, DUB can occur in women who are ovulating. In these cases, periods are usually heavy or prolonged but occur at regular intervals (i.e., menorrhagia).<sup>7</sup>

Anovulatory DUB accounts for more than 70 percent of cases of dysfunctional uterine bleeding<sup>8</sup> and results from unopposed estrogen stimulation in the endometrium. In anovulation, estrogen is continually

secreted but progesterone, which normally counteracts uterine lining proliferation, is not produced. In patients who have anovulatory DUB, the endometrium undergoes continuous growth, becomes vascular and fragile, and sloughs irregularly.

Although it may occur in women of any age, anovulatory bleeding is most prevalent among women who are in their perimenarchal or perimenopausal years.<sup>1,3</sup> In adolescents, the immature hypothalamic-pituitary axis may fail to appropriately respond to estrogen and progesterone stimulation in the first 18 months after menarche, resulting in anovulation and irregular bleeding. As menopause approaches, a decline in estradiol levels and progesterone production may result in decreased hypothalamic feedback, leading to anovulation and irregular shedding of the endometrium.<sup>9</sup>

The mechanisms of ovulatory DUB are not well understood, but in some cases it may result from a presumed luteal phase deficiency. A deficient luteal phase, shortened by insufficient progesterone production, may coexist with high, low or normal estrogen levels, leading to a disruption of the hypothalamic-pituitary-ovarian functioning and resulting in AUB. With ovulatory cycles, menorrhagia, polymenorrhea or oligomenorrhea may occur.<sup>10</sup>

### Differential Diagnosis

In order to establish a diagnosis of DUB, it is important to rule out pregnancy, systemic diseases and pelvic pathology. Effective management of AUB is highly dependent on its etiology; therefore, a detailed history and careful evaluation of the patient are useful in determining the cause of bleeding and the most appropriate treatment options.

Evaluation of women who present with AUB should begin with a thorough medical history, including gynecologic and sexual history, and any associated symptoms. Although perceived blood loss often does not correlate with actual quantitative measurements of menstrual flow,<sup>1,11</sup> a detailed menstrual history, including the number of pads or tampons used per day, may be helpful.

**Table 1. Terms Used to Describe Patterns of Abnormal Uterine Bleeding**

Terms	Definitions
Menorrhagia	Prolonged (> 7 days) or excessive (> 80mL) uterine bleeding occurring at regular intervals
Metrorrhagia	Uterine bleeding occurring at irregular intervals or between periods
Menometrorrhagia	Uterine bleeding occurring at irregular intervals, with heavy (> 80mL) or prolonged (> 7 days) menstrual flow
Polymenorrhoea	Uterine bleeding occurring at regular intervals of < 21 days
Oligomenorrhoea	Uterine bleeding occurring at intervals of 35 days or longer
Amenorrhoea	Absence of uterine bleeding for 6 months or longer in a nonmenopausal woman

Information from references: 1, 7, 10, 13.

Because unopposed estrogen stimulation resulting from anovulatory menstrual cycles represents an increased risk for endometrial cancer,<sup>12</sup> a menstrual history is important to distinguish between prolonged and irregular menses. A menstrual calendar may be useful in establishing the general pattern of bleeding and determining whether or not a woman is ovulating.

A list of prescription and over-the-counter medications can help identify whether the patient is taking drugs that may induce bleeding, such as anticoagulants, antipsychotics, tricyclic antidepressants, corticosteroids and hormonal medication.<sup>7,10</sup> Nonprescription medications and herbal supplements can also affect bleeding patterns. For example, when taken in combination with aspirin, Ginkgo biloba may increase the risk of bleeding and play a role in menorrhagia.<sup>2</sup> Ginseng, black cohosh and soy supplements may alter estrogen levels or clotting parameters and cause menstrual irregularities.<sup>10</sup>

It is important to exclude the possibility of pregnancy even in the absence of a reported history of sexual activity or in the perimenopausal patient.<sup>2</sup> A pregnancy test is recommended in women of reproductive age, especially if a careful bimanual pelvic examination detects uterine enlargement.<sup>10</sup> Pelvic examination and palpation of the vagina are also helpful in the detection of anatomic bleeding sites and signs of infection, polyps, leiomyomata, tears or malignancy.<sup>2</sup>

### Laboratory Tests

Laboratory and diagnostic tests may be appropriate depending on the patient's age and clinical clues from medical history and physical examination. For instance, approximately 20 percent of adolescents who have persistent menorrhagia have an underlying systemic disease, and more than 50 percent of these patients have a coagulopathy such as von Willebrand's disease, thrombocytopenia or leukemia.<sup>19</sup> Thus, if the patient has a family history of a bleeding disorder or if signs of coagulopathy such as severe menstrual bleeding, frequent bruising, and nose and gum bleeding are present, a complete blood count with platelet count<sup>10</sup> should be used to assess volume and duration of bleeding. A coagulation panel may be appropriate in perimenarchal patients who have severe bleeding and require hospitalization.<sup>2</sup>

In postmenarchal women, a complete history of Papanicolaou (Pap) smears is necessary to determine the risk for cervical dysplasia or cancer. If a patient has not been appropriately screened for

cervical cancer, a physical examination to check for any anatomic lesions along with a Pap smear should be performed when the patient is not actively bleeding. Any history of sexually transmitted infections (STIs), trauma or sexual abuse should be considered in the evaluation of the patient who has AUB. If the patient is sexually active or if symptoms of infection are present, cervical testing is recommended.

Obesity, acne and hirsutism may be signs of polycystic ovary syndrome (PCOS). PCOS is associated with insulin resistance, which may lead to anovulation and unopposed estrogen stimulation, and may result in AUB.<sup>10</sup> Slightly elevated androgen levels, such as testosterone and dehydroepiandrosterone sulfate (DHEA-S), are not uncommon in women who have PCOS. However, in women who show signs of sudden virilization or androgenism, serum testosterone and DHEA-S laboratory tests may be necessary to rule out testosterone-secreting ovarian or adrenal tumors.<sup>2,13</sup>

If galactorrhea is detected in the physical examination, a serum prolactin level is recommended to detect hyperprolactinemia, which can cause anovulation and irregular bleeding. Other endocrinopathies such as thyroid disorders should be considered and a thyroid-stimulating hormone (TSH) test may be appropriate in patients who report unexplained excessive weight gain, fatigue, constipation, hair loss or edema.<sup>2,11</sup>

### Other Diagnostic Tools

Although endometrial carcinoma is not common in women younger than 35 years of age, the need for endometrial assessment depends on each patient's risk factors. In women who have AUB and who are 35 years of age or older, it is important to rule out atypical endometrial hyperplasia or cancer. The incidence of endometrial cancer in 35- to 39-year old women is 6.1 cases per 100,000, more than double that of 30- to 34-year-old women, and it increases to 36.5 cases per 100,000 in women aged 40 to 49 years.<sup>7</sup> Other risk factors for endometrial cancer include nulliparity, obesity, type 2 diabetes, tamoxifen (Nolvadex) therapy and anovulatory cycles.<sup>10,12</sup>

Dilatation and curettage (D&C) is a diagnostic procedure generally used for stabilization in acute episodes of uterine bleeding.<sup>3</sup> D&C used to be the gold standard for diagnosing endometrial cancer. However, less than half of the uterine cavity is curetted in approximately 60 percent of D&C procedures performed.<sup>14</sup> Thus, focal intracavity lesions may be missed when blind curettage is performed, and a significant false-negative rate is associated with D&C. When performed in conjunction with hysteroscopy, which allows for direct visualization of the uterine cavity, the diagnostic accuracy of D&C may be improved, since any abnormalities found can be immediately biopsied and completely removed.<sup>15,16</sup>

Endometrial biopsy is an accurate and commonly used diagnostic test, with an endometrial cancer detection rate of 91 percent and a 2 percent false-positive rate in premenopausal women.<sup>14,17</sup> Its sensitivity improves to 97 percent when it is performed in combination with saline infusion sonohysteroscopy (SIS),<sup>17,18</sup> which is a more accurate procedure than endometrial biopsy in the diagnosis of intracavity lesions.

If abnormal menstrual bleeding persists despite a negative endometrial biopsy and SIS, hysteroscopy should be considered.<sup>17,19</sup> Hysteroscopy can be performed in the office setting and, in some cases, may actually eliminate the need for D&C. Hysteroscopy is more sensitive than fractional D&C, especially when used to diagnose polyps and submucous fibroids. When combined with endometrial biopsy, the accuracy of hysteroscopy reaches almost 100 percent in the diagnosis of endometrial dysplasia and cancer.<sup>20</sup>

In postmenopausal women whose endometrium is stable and who are experiencing AUB, who are unresponsive to medical therapy and who are at low risk for endometrial cancer, a transvaginal ultrasonography (TVUS) may be a noninvasive alternative to D&C in the detection of intracavity lesions.<sup>10</sup> Postmenopausal women found to have an endometrial stripe thickness greater than 5 mm may need further evaluation.<sup>16,21</sup>

However, TVUS is not as effective as SIS in the detection of polyps, submucous fibroids and focal intracavity lesions such as endometrial hyperplasia.<sup>10</sup> Additionally, ultrasonography as well as SIS are of limited utility in the specification of abnormal findings and cannot always reliably distinguish between benign proliferation, hyperplasia, polyps and carcinoma.<sup>16</sup> Women who have any visible vaginal and/or cervical lesions should undergo colposcopy and biopsy, even if they have a negative Pap smear, and especially if they are menopausal, postmenopausal or at high risk for endometrial cancer.<sup>2</sup>

### Management of DUB

Once a diagnosis of DUB has been established, the goal of management is to stabilize bleeding and treat underlying hormonal and endometrial abnormalities.<sup>12</sup> Treatment choices depend on the severity and type of bleeding, fertility status of the patient and contraception needs. Long-term side effects and the patient's circumstances and preferences should also be taken into consideration.

### Severe Bleeding

Conjugated equine estrogen therapy (Premarin) is very effective in the management of severe, acute bleeding. It can be administered intravenously (25 mg every four hours for 24 hours) or orally in divided doses up to 10 mg per day. Intravenous conjugated equine estrogen therapy acts more rapidly to stop vaginal bleeding,<sup>22</sup> while oral administration of such high doses may be poorly tolerated, usually because of nausea.<sup>11</sup> Other effective therapies for the treatment of severe, acute episodes of uterine bleeding include esterified estrogens (Menest), synthetic conjugated estrogens (Cenestin), estropipate

(Ogen, Ortho-Est), estradiol (Estrace, Gynodiol) and estradiol valerate in oil (Delestrogen). In patients who do not respond to emergency intravenous therapy, D&C should be considered.<sup>9</sup>

Once the acute bleeding episode has been stabilized, a regimen of one monophasic oral contraceptive pill (OCP) twice daily for five to seven days should be administered until bleeding stops. This regimen usually controls bleeding within 24 hours to 48 hours. Withdrawal bleeding should then occur once therapy is discontinued. On the fifth day of bleeding, a new 28-day packet of low-dose cyclic OCPs should then be started and therapy continued for three to six months to correct anemia.<sup>23</sup> Medroxyprogesterone acetate (Provera) may also be administered at a dose of 10 mg per day for the last 10 days of the cycle to produce withdrawal bleeding.<sup>9</sup> In patients who have no clear bleeding pattern, it may be given at the time of visit, with the 10-day administration pattern being repeated monthly for at least three menstrual cycles.

### Pharmacologic Treatments for Nonemergent Menstrual Bleeding

Most family physicians are familiar and comfortable with treating AUB medically with OCPs, and this is the preferred treatment.<sup>13</sup> OCPs induce endometrial atrophy and regulate the menstrual cycle, helping to prevent the risks associated with prolonged unopposed estrogen stimulation. In cases of more severe bleeding, OCPs may be administered two to four times a day for five to seven days or until bleeding stops. In milder cases, therapy may start with one pill a day. In either case, treatment should continue until all pills in the packet are finished. Withdrawal bleeding should occur when active pills are discontinued.

Progestogens reduce menstrual blood loss by suppressing endometrial growth and maturing the existing functionalis layer of the endometrium. When administered for 21 days of the menstrual cycle, progestogens have been shown to be an effective alternative to OCPs in the treatment of menorrhagia. However, progestogens are less effective than other medical therapies at reducing menstrual bleeding in women who have menorrhagia when administered during the luteal phase of the menstrual cycle.<sup>24</sup> Side effects such as breast tenderness, bloating, headaches,

mood changes and breakthrough bleeding may also make long-term treatment with progestogens less acceptable.<sup>25</sup>

Menorrhagia can also be treated with the levonorgestrel-releasing intra-uterine system (LRIS [Mirena]).<sup>10</sup> The LRIS releases low doses of progestogenic hormone, which suppresses endometrial proliferation, significantly reducing menstrual blood loss. Although patients may experience side effects such as weight gain, breast tenderness and bloating, the device is generally well tolerated and satisfaction rates are similar to those reported by women who have undergone endometrial resection or thermal balloon ablation.<sup>25</sup>

Studies regarding the effects of nonsteroidal anti-inflammatory drugs (NSAIDs) in the treatment of menorrhagia are small, and more data to determine their efficacy are needed. However, NSAIDs such as naproxen (Naprosyn) and mefenamic acid (Ponstel) may

**Table 2. Diagnostic Tools for the Evaluation of AUB**

Laboratory tests, imaging and tissue sampling	Conditions
Beta-subunit human chorionic gonadotropin (urine or serum)	Pregnancy
Complete blood count with platelet count and coagulation studies	Coagulopathy
Thyroid-function tests	Hypothyroidism, hyperthyroidism
Prolactin	Pituitary adenoma
Blood glucose	Diabetes mellitus
DHEA-S, serum testosterone if virilized	Ovarian or adrenal tumor
Papanicolaou smear	Cervical dysplasia or cancer
Cervical testing for infection	Cervicitis, PID
Endometrial biopsy or dilatation and curettage	Endometrial hyperplasia, atypia or adenocarcinoma
Transvaginal ultrasonography	Pregnancy, ovarian or intracavity lesions
Saline-infusion sonohysterography	Intracavity lesions, polyps, submucous fibroids, endometrial hyperplasia
Hysteroscopy	Intracavity lesions, polyps, submucous fibroids, endometrial hyperplasia, endometrial cancer

DHEA-S = dehydroepiandrosterone sulfate; PID = pelvic inflammatory disease.

Adapted from *Abnormal Uterine Bleeding*, published in the April 15, 2004 issue of *American Family Physician*. Copyright © AAFP. All rights reserved.

decrease uterine bleeding by reducing prostaglandin levels.<sup>4,10</sup> Naproxen (500 mg twice a day) or mefenamic acid (an initial dose of 500 mg followed by 250 mg every six hours) may be safely administered.

Antifibrinolytic agents such as tranexamic acid (Cyklokapron) have been shown to significantly reduce heavy menstrual bleeding by inhibiting the breakdown of blood clots (fibrinolysis),<sup>25,26</sup> although this represents an off-label use. Although there is concern about these agents causing thrombotic disorders,<sup>10</sup> studies in Europe have shown that the rate of incidence of thrombosis in women who are treated with tranexamic acid is comparable with the spontaneous frequency of thrombosis in women.<sup>26</sup> More studies are needed to determine their safety, tolerability and efficacy when used to treat heavy menstrual bleeding.

Danazol (Danocrine) suppresses estrogen and progesterone receptors in the endometrium, leading to endometrial atrophy and reduced menstrual bleeding. Similarly, leuprolide acetate (Eligard, Lupron, Viadur) is used off-label to induce a hypogonadotropic state and amenorrhea. However, because of their side effects, danazol and leuprolide acetate are indicated only when hormonal therapy fails or is contraindicated.<sup>3,7</sup> Danazol or leuprolide acetate may be prescribed prior to endometrial resection or ablation or hysterectomy, as they promote endometrial atrophy, improving operating conditions for the surgeon and short-term postoperative outcomes.<sup>27</sup>

**Nonpharmacologic Treatments**

Surgical treatment of AUB is generally reserved for cases in which the patient no longer desires to conceive, does not tolerate or respond to pharmacologic therapy, situations when pharmacologic therapy is contraindicated or when it is the woman's preference and physician's recommendation.

Hysterectomy is the definitive treatment for ovulatory and anovulatory DUB. The surgery can be performed vaginally, abdominally and laparoscopically, with vaginal hysterectomy being associated with fewer complications and shorter recovery time. Patient satisfaction rates after hysterectomy tend to be

**Practice Recommendation:** Progestogen therapy for 21 days of the cycle results in significant reduction in menstrual blood loss.



**Available at:** <http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD001016/frame.html>

**Strength of Evidence:** The evidence supporting this recommendation is based on a meta-analysis of seven randomized controlled trials involving 252 participants.

**Practice Recommendation:** Antifibrinolytic therapy (tranexamic acid and mefenamic acid) causes a greater reduction in objective measurements of heavy menstrual bleeding when compared to placebo or other medical therapies (NSAIDs, oral luteal phase progestogens and ethamsylate).

**Available at:** <http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD000249/frame.html>

**Strength of Evidence:** The evidence supporting this recommendation is based on a meta-analysis of seven randomized controlled trials involving 193 participants.

**Practice Recommendation:** Endometrial destruction offers an alternative to hysterectomy as a surgical treatment for heavy menstrual bleeding.

**Available at:** <http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD000329/frame.html>

**Strength of Evidence:** The evidence supporting this recommendation is based on a meta-analysis of five randomized controlled trials involving 752 participants.

high,<sup>25</sup> but it is a major surgical procedure and DUB is usually not a life-threatening condition. When compared with other surgical alternatives, the postoperative recovery time of hysterectomy is lengthy, and the procedure is associated with a high incidence of short-term complications such as hemorrhage and infection.<sup>25</sup>

Compared with hysterectomy, endometrial ablation is a less invasive, uterus-sparing alternative that is cost-effective. The need for general anesthetic is reduced, postoperative complications are fewer and recovery time is shorter.<sup>28</sup>

First-generation endometrial ablation techniques involve the use of a hysteroscope to aid in the visualization of the uterus,

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and electrocautery or laser tools are used to destroy the endometrium. Endometrial ablation performed using these techniques is less risky than hysterectomy, but there is still a small risk of uterine perforation, infection and hemorrhage.<sup>25</sup> Women who undergo endometrial ablation procedures in which these techniques are used may still require a general or regional anesthetic and, often, a short stay at the hospital.

The risks of hemorrhage and uterine perforation have been reported to be lower when second-generation techniques for endometrial ablation, such as thermal balloon (Thermachoice), microwave (Microsulis), cryoablation (Her Option) or radiofrequency (Novasure), are used.<sup>17</sup> Second-generation ablation techniques have been found to be as effective as first-generation techniques and may be performed on an outpatient basis under local anesthetic. Although the equipment required for this procedure is more sophisticated and expensive than that used in older ablative techniques, the skills required of the operator are less specialized.<sup>25</sup>

More data on the safety, reliability and cost-effectiveness of these techniques are needed, but currently available evidence suggests that the thermal balloon and the microwave methods are associated with minimal complication rates.<sup>25</sup> The main disadvantage of conservative surgery in comparison with hysterectomy seems to be the potential for symptom recurrence. A 2007 Cochrane systematic review of controlled randomized trials comparing treatment options for heavy menstrual bleeding reported that the percentage of women who returned for additional surgery to treat menstrual problems within five years of having undergone endometrial resection or ablation ranged from 4 percent to 27 percent.<sup>25</sup>

Regardless of the possible need for retreatment, some patients may prefer the convenience and short recovery times associated with endometrial ablation, while others may opt for the certainty afforded by complete hysterectomy. Ultimately the family physician's role is to help patients understand and balance the risks and benefits associated with each treatment option.

Article references are available online at <http://www.aafp.org/cmebulletin>, or call (800) 274-2237, ext. 6531, for a faxed copy.

# CMEBulletin

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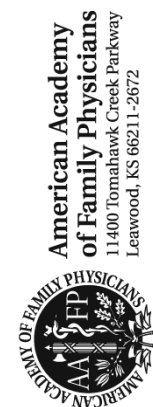
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# Self-Assessment Quiz

- True or false: Although dysfunctional uterine bleeding (DUB) may occur in women of any age, anovulatory DUB is less common in women who are in their perimenarchal and perimenopausal years.  
A. True  
B. False
- Which one of the following statements regarding the evaluation of abnormal uterine bleeding (AUB) is true?  
A. Excluding the possibility of pregnancy is unnecessary in patients who deny sexual activity or in perimenopausal women.  
B. Since perceived blood loss often does not correlate with actual quantitative measurements of menstrual flow, a menstrual history is not helpful in the evaluation of patients who complain of heavy menstrual bleeding.  
C. When combined with endometrial biopsy, hysteroscopy is highly accurate in the detection of endometrial dysplasia and endometrial cancer.  
D. Endometrial assessment, including endometrial biopsy, is recommended in all patients who present with AUB, regardless of other risk factors for endometrial cancer.
- Which one of the following statements regarding pharmacologic interventions for the treatment of patients who have DUB is true?  
A. Although antifibrinolytic agents have been shown to significantly reduce menstrual blood loss, their use in the treatment of menorrhagia is limited because of their association with thrombotic disorders.  
B. In cases of acute, severe episodes of uterine bleeding, oral administration of conjugated equine estrogen therapy is the first line of treatment.  
C. When administered during the luteal phase of the menstrual cycle, progestogens are highly effective in the management of heavy menstrual bleeding.  
D. Side effects such as breast tenderness, weight gain and bloating make the levonorgestrel-releasing intrauterine system (LIRS) a poorly tolerated alternative for patients who have DUB.
- True or false: Danazol (Danocrine) and leuprolide acetate (Eligard, Lupron, Viadur) promote endometrial atrophy and are effective when prescribed prior to endometrial resection or ablation to improve operating conditions and short-term postoperative outcomes.  
A. True  
B. False
- Which one of the following statements regarding nonpharmacologic interventions for the treatment of patients who have DUB is true?  
A. High patient satisfaction rates make surgical procedures such as endometrial ablation or hysterectomy the first line of treatment in patients who have DUB.  
B. When compared with abdominal or vaginal hysterectomy, laparoscopic hysterectomy is associated with shorter postoperative recovery time and fewer complications such as hemorrhage and infection.  
C. In addition to being the definitive treatment for DUB, hysterectomy is associated with a lower incidence of postoperative complications when compared with endometrial ablation.  
D. Second-generation endometrial ablation techniques can be performed as outpatient procedures with a local anesthetic, and are considered less invasive, cost-effective alternatives to hysterectomy.

Answers: 1.B,2.C,3.A,4.B,5.D

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Note: On this scale, 5 is the highest rating, 1 is the lowest.

Relevance of topic to my practice	5	4	3	2	1
Currency of clinical information	5	4	3	2	1
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Overall rating	5	4	3	2	1

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### Answers (Please circle one):

- |            |            |
|------------|------------|
| 1. A B     | 4. A B     |
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| 3. A B C D |            |

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