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WOMEN'S HEALTH

Vol-4 No-1 March-May 2011

Editorial Note:

Dear Doctor,

It's our immense pleasure to inform you that we have published our newsletter, "Women's Health". In this issue we are focusing on the Maternal activity restriction and the prevention of preterm birth & Expectant management of first-trimester miscarriage. Your comments and suggestions will enrich our upcoming issues. Please participate in quiz competition and win prizes.

Dysfunctional Uterine Bleeding

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Dysfunctional Uterine Bleeding

Introduction

Dysfunctional uterine bleeding (DUB) is defined as abnormal uterine bleeding caused by a hormonal mechanism. Any alteration of the normal menstrual cycle mechanisms can lead to steady-state estrogen production and DUB.

The Normal Menstrual Cycle

The events of the menstrual cycle are shown in Figure 1. The first day of a typical cycle (day l) corresponds to the first day of menses. The menstrual phase usually lasts 4 days and involves the disintegration and sloughing of the functionalis layer of the endometrium. Prostaglandins are involved in regulation of menses, with prostaglandin F2-alpha causing myometrial contractions and vasoconstriction, and prostaglandin E2 causing vasodilitation and muscle relaxation.

The proliferative (follicular) phase extends from day 5 to day 14 of the typical cycle. It is marked by endometral proliferation brought on by estrogen stimulation. The estrogen is produced by the developing ovarian follicles under the influence of follicle stimulating hormone (FSH). There is marked cellular proliferation of the endometrium and an increase in the length and convolutedness of the spiral arteries. Endometrial glands develop and contain some glycogen. This phase ends as estrogen production peaks (must be greater than 200 pg/ml for more than 24 hours), triggering the FSH and luteinizing hormone (LH) surge. Rupture of the ovarian follicle follows, with release of the ovum (ovulation).

The secretory (luteal) phase is marked by production of progesterone and less potent estrogens by the corpus luteum. It extends from day 15 to day 28 of the typical cycle. The functionalis layer of the endometrium increases in thickness, and the stroma becomes edematous. The glands become tortuous with dilated lumens and stored glycogen. If pregnancy occurs, the placenta produces human chorionic gonadotropin (HCG) to replace progesterone, and the endometrium (and pregnancy) is maintained.

If pregnancy does not occur, the estrogen and progesterone feed back to the hypothalamus, and FSH and LH production falls. The spiral arteries become coiled and have decreased blood flow. At the end of this period, they alternately contract and relax, causing disintegration of the functionalis layer and menses.

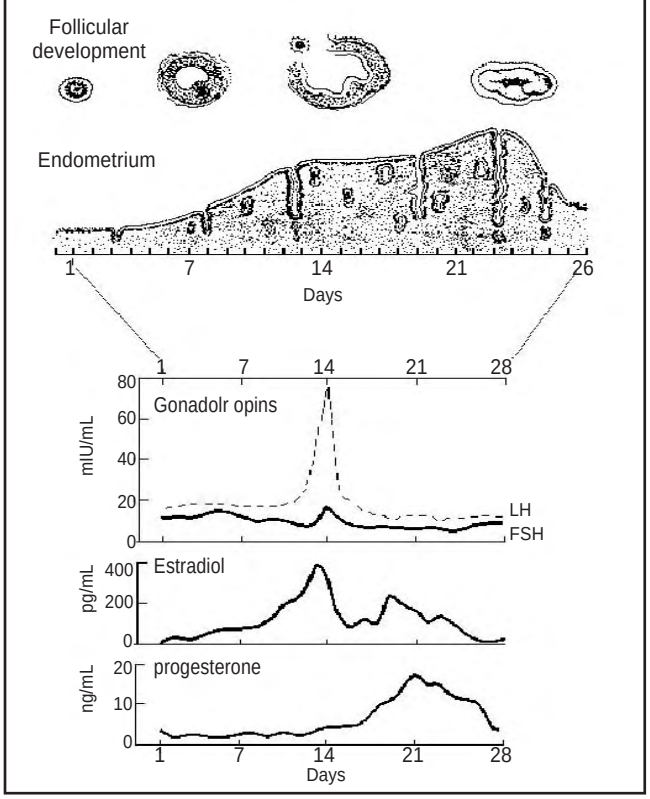
Terms

- Normal menstruation - regular cyclic uterine blood flow lasting 2 to 6 days with an interval of 21 to 35 days and a typical blood loss of 20 to 60 ml.
- Menorrhaga - prolonged or excessive uterine bleeding occurring at regular intervals.
- Metrorrhaga - uterine bleeding occurring at irregular and more frequent than normal intervals.
- Menometrorrhagia - prolonged or excessive uterine bleeding occurring at irregular and more frequent than normal intervals (the 2 above combined.)
- Intermenstrual bleeding - (commonly called "spotting") uterine bleeding of variable amounts occurring between regular menstrual periods.
- Polymenorrhea - uterine bleeding occurring at regular intervals of less than 21 days.
- Oligomenorrhea - uterine bleeding occurring at intervals of 35 days to six months.
- Amenorrhea - no uterine bleeding for 6 months or longer.

Pathophysiology

DUB is most common near the beginning and end of a woman's reproductive life, but may occur at any time. In the first 18 months after menarche, the immature hypothalamin-pituitary axis may fail to respond to estrogen

Figure 1. The menstrual cycle, showing pituitary and ovarain hormones and histologic changes.



and progesterone, resulting in anovulation. In obese women, the non-ovarian endogenous estrogen production may upset the normal menstrual cycle. As menopause approaches, decreases in hormone levels or in responsiveness to hormones also may lead to anovulatory DUB. Potential causes of vaginal bleeding are shown in Table 1.

Most cases of DUB are caused by anovulatory cycles that result in high steady-state estrogen with no progesterone. The continuous estrogen stimulation causes continuous development of the functionalis layer until estrogen feedback produces a slow drop in FSH. Eventually, the blood supply is outgrown and parts of the endometrium slough. Estrogen, however, promotes healing of the endometrium so some parts are always healing as others slough, resulting in menometrorrhagia.

A luteal phase deficiency also may result in DUB. It is characterized by a shortened luteal phase from insufficient progesterone production or effect. The insufficient progesterone stimulation may be coexistent with high, low, or normal estrogen levels and often will result in similar problems in anovulatory cycles. This problem, along with the loss of LH surge, may be especially prominent in amenorrheic athletes.

Another mechanism of DUB, especially in patients who are 40 years old and older, is diminishing number and quality of ovarian follicles. Follicles continue to develop but do not produce enough estrogen in response to FSH to trigger ovulation. Estrogen continues to be produced, which usually results in late cycle estrogen breakthrough bleeding.

Improper balance of estrogen and progesterone may result in DUB. It may result in low estrogen states from low-dose oral contraceptive pills (OCPs), resulting in insufficient build up of stable endometrial lining, with resultant prolonged light bleeding. DUB can also be caused by high progestin activity oral contraceptive pills. These patients will often need a higher level of estrogen or a lower activity progestin. Bleeding irregularities are very common with the Norplant System, depomedroxyprogesterone injection, and the "mini pill," which is often the reason these contraceptives are discontinued. Nonprogestin-containing IUDs also may cause DUB. Nonsteroidal antiinflammatory drugs (NSAIDS) or supplemental estrogen as described below may help with this sideeffect.

Endocrine disorders also may cause DUB. Hyperprolactinemia inhibits production and release of gonadotropin-releasing hormone. Polycystic ovary disease often presents as anovulatory cycles resulting in DUB. Hypothyroidism, hyperthyroidism, and Cushing's disease can be associated with DUB. Finally, premature ovarian failure may be a factor in patients who present with DUB.

Postcoital bleeding usually indicates a structural lesion of the cervix or vagina. Infectious etiologies such as chlamydia and gonorrhea must be excluded or treated. Uterine or cervical polyps also may be a source of bleeding. Dysplastic or malignant lesion of the cervical or vaginal epithelium may cause irregular or postcoital bleeding.

An enlarged uterus may be caused by adenomyosis, uterine fibroids, endometriosis, or pregnancy. Submucosal myomas and endometrial polyps are associated with DUB in both premenopausal and postmenopausal women. Ectopic pregnancy and pregnancy complications also must be ruled out. A high index of suspicion for the possibility of pregnancy must be maintained. Endometrial cancer should be excluded, especially in older and high-risk patients with this symptom.

Table 1. Causes of dysfunctional uterine bleeding.

Endocrine Cushing's disease immature hypothalamin-pituitary axis hyperprolacinemia hypothyroidism menopause obesity polycystic ovary disease premature ovarian failure	Infections chlamydia gonorrhea PID
Stuctural lesions adenomyosis coagulopathies condyloma acuminata dysplastic or malignant lesion of the cervix or vagina endometiosis endometrial cancer uterine or cervical polyps uterine leiomyomata trauma	Medications hormonal agents low-dose oral contraceptive pills (OCPs) nonprogestin-containing IUDs nonsteroidal anti-inflammatory drugs (NSAIDS) Norplant System progestin-only contraceptive (the "mini pill") tamoxifen warfarin
	Pregnancy ectopic pregnancy incomplete abortion pregnancy complications

Table 2. Risk factors for endometrial cancer. (RR = relative risk)

Age - 75% of cases occur after menopause with peak incidence in the late 60s.	RR (age > 60 years) = 5.2
Obesity - especially upper body fat. This may be secondary to increased estrogen production and bioavailability.	RR= 3 to 10
Polycystic ovary disease.	RR = 5.2
Unopposed exogenous estrogen.	RR = 2 to 14
When progestins are added (oral contraceptives or with replacement therapy), relative risk is less than for the general population.	RR= 0.5 to 1
Diabetes (all types grouped).	RR = 2 to 2.8
Personal or family history of ovarian or breast cancer. Women who are overweight and have had breast cancer are at even greater risk.	
Nulliparity.	RR = 1.3
Late menopause.	RR (entering menopause after age 52) = 2.5
Tamoxifen therapy - Use for greater than one year is an independent risk factor.	RR = 7.5

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Table 3. Laboratory tests to consider for DUB. Testing should be individualized based on each patiet's history and physical findings.

Test	Indication (to rule out)
urine pregnancy test	pregnancy
CBC	anemia
PT/PTT	coagulpathy (especially in adolescents
Pap smear*	cervical cancer
FSH	> 40IU/L suggests ovarian failure
liver function tests	liver disease
TSH	thyroid disease
prolactin level	pituitary adenoma (with breast discharge)
DHEAS	polycystic ovary disease

* if there is no evidence of infection and it is indicated

Endometrial Cancer

One of the most important goals in work-up of DUB is to rule out endometrial cancer, especially in older women. Development of endometrial cancer is related to estrogen stimulation and endometrial hyperplasia. Risk factors are shown in Table 2. Symptoms include postmenopausal bleeding, which is usually considered endometrial cancer until proven otherwise. Bleeding prevalence may be as high as 1/3 of cases, and the presence of uterine myomas should NOT delay appropriate work-up. Other symptoms may include metrorrhagia, lower abdominal pain or pressure, and (rarely) back pain or lower extremity edema secondary to metastasis.

Clinical findings most commonly are a normal exam of vagina, uterus, and cervix, although advanced disease may be associated with enlarged uterus or pelvic mass. Cervical and vaginal metastasis can cause cervical stenosis, pyometra, or a mucosanguineous vaginal discharge. Regional metastasis may present as a bladder or rectal mass.

Evaluation

Evaluation of DUB emphasizes establishing the cause and ruling out endometrial cancer. A typical algorithm (Figure 2) begins with a thorough history. Important factors to document include patient's age, last menstrual period, last normal menstrual period, amounts and duration of bleeding, postcoital bleeding, medications (especially hormonal agents, NSAIDS, or warfarin), history of any endocrine abnormalities, symptoms of pregnancy, symptoms of coagulopathies, contraceptive history, and history of trauma.

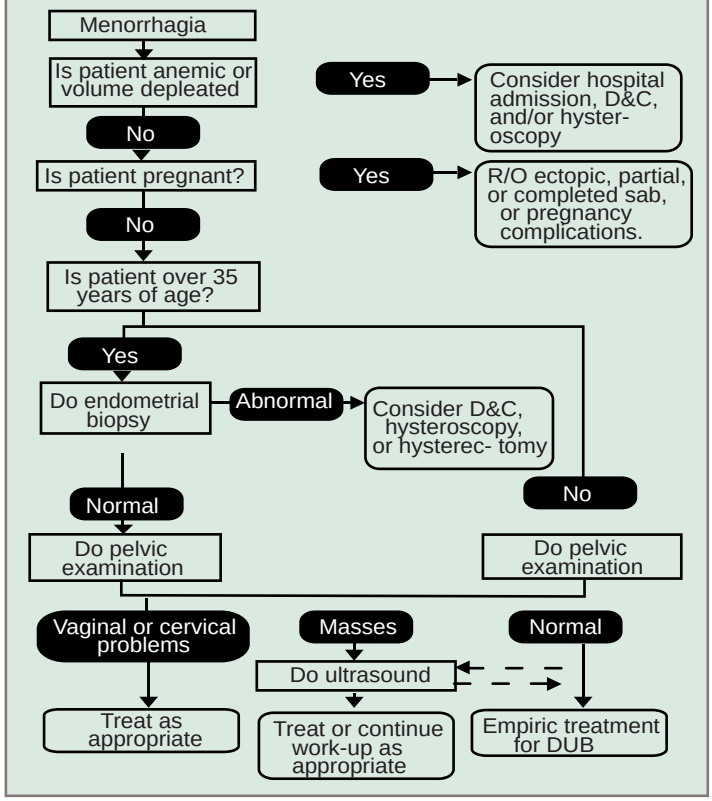
General physical examination should focus on symptoms of endocrinopathies, including polycystic ovary disease (including obesity and hyperandrogenism), hyperprolactinemia, and hypothyroidism. Pelvic examination is unnecessary in oligomenorrheic patients who are not sexually active and are within 18 months of menarche. Otherwise, gynecologic examination includes inspection of the vagina and cervix for physical lesions (polyps, leiomyomata, tears, malignancy, or incomplete abortion) or infection. The size, shape, position, and firmness of the uterus should be examined. Note any signs of excessive blood loss.

Basal temperature charting may assist in determining when and whether ovulation occurs, if the patient will cooperate with testing. The patient may take her temperature any time during the day as long as she is consistent from day to day. A rise in basal temperature of 0.3ø C to 0.6ø C is indicative of ovulation. This determination may also be made using serum progesterone determination in the luteal phase, with a level greater than 3 mg/mL indicating ovulation has occurred.

Diagnostic Tests

Endometrial biopsy (EMB) is the most commonly used diagnostic test for DUB. It provides an adequate sample for diagnosis of endometrial problems in 90% to 100% of cases, but may fail to detect polyps and leiomyomas. It is indicated in all women with DUB who are 35 years of age or older, since their risk of developing malignancy is much higher. Any woman with amenorrhea for one year or longer who experiences uterine bleeding also should have an EMB. The newer slim endometrial suction currettes (Pipelle) produce samples comparable to older, more traumatic methods but with less pain. Sampling should be performed late in the cycle if possible, so it can be

figure 2. Evaluation of menorrhagia and dysfunctional uterine bleeding



determined if ovulation has taken place.

Uterine ultrasound, especially transvaginal ultrasonography (TV-US), can give information about suspected structural problems including fibroid tumors. It is classically indicated when physical exam indicates anatomic gynecologic abnormalities, especially of the ovaries where other methods provide poor information. The endometrial stripe assessment on TV-US can provide information about the ovulatory stage of the endometrium that has a 93% correlation with hystological diagnosis. An endometrial thickness measurement of less than 4 to 7 mm is rarely associated with cancer, and endometrial sampling may not be necessary in such patients.

Dilatation and curettage (D&C) allows more extensive sampling of the uterine cavity and has the advantage of being both diagnostic and therapeutic. It may be the treatment of choice when bleeding is severe or necessitates blood transfusions. It has a higher sensitivity than endometrial biopsy, especially with smaller in-situ lesions. It is often used when EMB is inadequate, the cervical os is stenotic, or DUB treatment fails. When D&C is combined with endometrial biopsy, the detection rate approaches 100%. Fractional D&C is usually not used in teenagers, because they rarely have endometrial cancer and the procedure may damage the cervix or uterus. It is currently required for the staging of occult cancer.

Hysteroscopy can be used in place of D&C for most indications, and allows for direct visualization of the endometrial cavity with directed biopsy. Hysteroscopy is more sensitive than fractional D&C, especially at diagnosing polyps and submucosal leiomyomas, but it may miss endometritis. When combined with EMB, it has almost 100% accuracy in diagnosing endometrial dysplasia and cancer. It may eventually become required for staging of occult cancer. Like EMB, it often can be performed in the office setting and may be used for treatment of DUB.

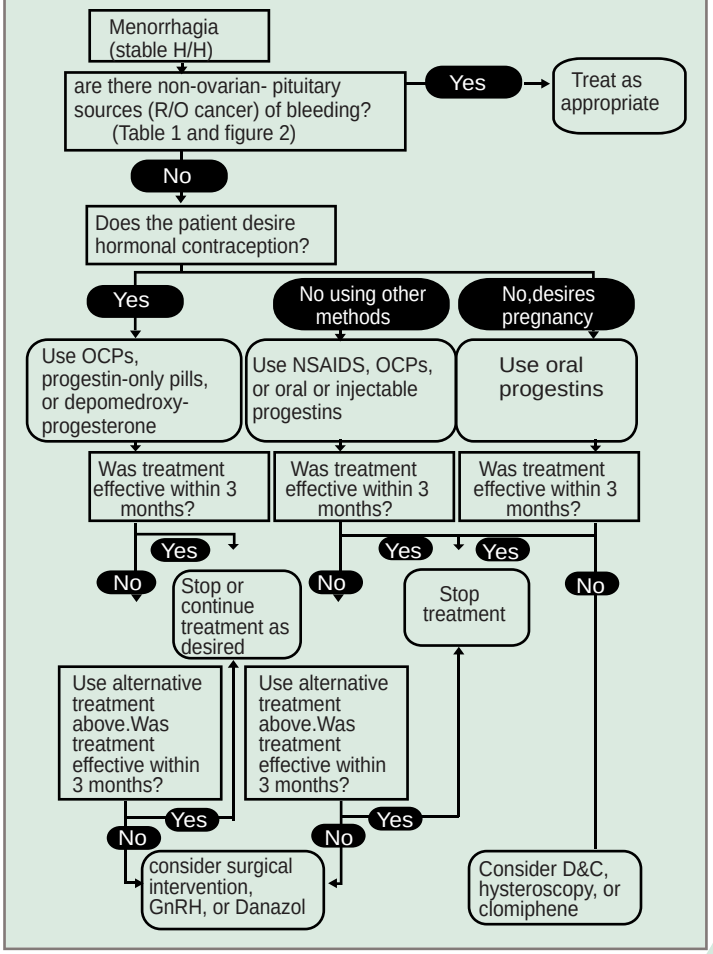
Treatment

There are medical, surgical, and combined methods of treating DUB. The choice of approach depends on the cause, severity of bleeding, patient's fertility status, need for contraception, and treatment options available at the care site. A typical algorithm for the treatment of mild to moderate DUB is shown in Figure 3. The pharmacological treatment options for mild to severe DUB are given in table 4 and indvidual drugs are discussed in table 5.

Cases of acute, heavy, uncontrolled bleeding should be treated with intravenous estrogen, 25mg every 4 hours, to a maximum of 3 doses or until bleeding stops (Table 5.) Oral conjugated estrogen also may be given in divided doses up to 10mg per day, although this regimen often causes nausea and vomiting. In less severe cases, conjugated estrogens at doses of 2.5 to 5mg per day stops the bleeding over 24 to 48 hours. Regardless of which regimen is used, it should be followed by conjugated estrogen at 1.25 to 2.5mg plus 10mg of medroxyprogesterone per day for about 10 days. Withdrawal bleeding should then occur as all drugs are withdrawn. In postmenopausal women, continuous estrogen therapy with conjugated estrogens (0.625 - 1.25mg) plus cyclic medroxyprogesterone (10 mg) for 10 - 14 days of each month may be continued. This regimen works best in patients with atrophic epithelium.

In cases of moderately heavy DUB, oral contraceptive pills (OCPs) may be given up to four times a day for 5 to 7 days or until bleeding stops. The rest of the pills may then be taken once a day until the pack is finished and withdrawal bleeding occurs. In anovulatory patients, this is followed by an additional 2 months of OCPs as usually prescribed. This regimen will stabilize the epithelium, slough excessive build-up, and provide contraception. OCPs may also be started initially at one pill every day in milder cases of DUB. If the patient is already on OCPs and experiencing DUB, a change to a higher estrogen activity OPC is indicated.

Figure 3. Treatment of dysfunctional uterine bleedin.



Medroxyprogesterone (Provera) at 10mg PO per day for 10 to 12 days has traditionally been one of the most common methods used to control DUB. This "medical curettage" works well to correct midcycle spotting and when the EMB demonstrates proliferative endometruim. Depomedroxyprogesterone (150mg) or progesterone in oil (100 - 200mg) may be given intramuscularly to achieve similar effects. The progestin-only contraceptive pills also work well and, like depo-Provera, have the added benefit of providing contraception. Breast tenderness and mood swings are possible side-effects of therapy. These regimens work especially well with chronic or milder acute DUB. Progestin-containing IUDs, together with oral or transdermal estrogen, may control DUB in postmenopausal patients.

Nonsteroidal anti-inflammatory drugs (NSAIDS) can decrease DUB, probably through inihibition of prostaglandin synthesis. Naproxen 500mg twice daily, mefenamic acid 500mg three times daily, or ethamsylate 500mg four times a day has been shown to decrease menstrual flow. Once bleeding is controlled, NSAIDS need only be used during menstruation. These drugs are safe for long-term usage, and the long-term effects are well studied. Aspirin does not appear to be effective.

The androgenic synthetic steroid danazol, which is traditionally used to treat endometriosis, can be used to treat DUB. Similarly, the GnRH agonists goserelin acetate, leuprolide acetate, or nafarelin acetate induce a hypogonadotropic state which stops dysfunctional bleeding. They all produce hypogonadism and induce ammenorrhea. Because of their side effects, these drugs

are used when hormonal methods have failed or are contraindicated. These agents are primarily used to thin the endometrium prior to surgical intervention.

Dilatation and curettage (D&C) may ameliorate DUB, as well as diagnose potential dysplasia or malignancy. It is sometimes avoided in adolescents because of concerns about possible infertility. Repeated procedures may result in intrauterine adhesions.

Neodymium:yttrium-aluminum-garnet (Nd:YAG) laser endometrial ablation is a newer method of surgically treating the endometrium. It has a success rate of

Table 4 Medical treatment for dysfunctional uterine bleeding

Mild (bleeding is minimal and symptoms limited)

- NSAIDs, mefenamic acid 500mg TID for 3-5 days
- Medroxyprogesterone acetate 10 mg/d for 7-10 days each month
- Monophasic OCPs 35 mcg each day of the month, including inactive pills
- Levonorgestrel IUD
- Danazol 200-400mg/d

Moderate (moderate amounts of bleeding, mild anemia, and mild orthostatic symptoms or fatigue

- Medroxyprogesterone acetate 10 mg/d for 7-10 days each month
- OCPs BID for 5-7 days (flow should decrease in 24 - 48 hours), followed by 1 pill/d for the rest of the cycle for the next 3-6 months. Warn patients that flow will be heavy after the first pill pack, will decrease by 60% toward end of treatment period. Use an antiemetic with increased OCP dose
- Levonorgestrel IUD
- Danazol 200-400mg/d
- Antifibrinolytic agents (tranexamic acid, 1-1.5g 3 to 4 times per day)

Severe (heavy bleeding,moderate to severe anemia, significant orthostatic symptoms)

- OCPs as for moderate bleeding, with antiemetic for increased dose
- IV estrogen, 25 mg IV q 4 to 6 hours until bleeding stops or for 24 hours, followed by OCPs, Use with antiemetic medication
- Levonorgestrel IUD
- Danazol 200-400mg/d
- Antifibrinolytic agents (tranexamic acid, 1-1.5g 3 to 4 times per day)

IUD, Intrauterine device; NSAIDs, nonsteroidal - inflammatory drugs; oral contraceptive pills.

Table 5. Medical Therapies for DUB.

Therapy	Comments
Medroxyprogesterone (Provera) 10 mg PO/day for 10 to 12 days	Works well to correct midcycle spotting and when the EMB demonstrates proliferative endometrium.
Depo-medroxyprogesterone 150 mg IM every 3 months	Also provides contraception.
Progesterone in oil 100 - 200 mg IM	Also provides contraception.
Progestine-only oral contraceptives pills	For acute moderately heavy bleeding. The rest of the pills may then be taken Q day until the pack is completed, followed by an additional 2 months of OCPs.
Oral contraceptive pillls up to Qid for 5 to 7 days or until bleeding stops	For acute, heavy, uncontrolled bleeding.
Intravenous estrogen 25 mg Q4 hrs- - maximum of 3 doses or until bleeding stops	For acute, heavy, uncontrolled bleeding. Often causes nausea and vomiting. Should be followed by conjugated estrogen 1 .25 to 2.5 mg plus 10 mg of medroxyprogesterone per day for about 10 days.
Oral conjugated estrogen (Premarin) divided doses up to 10 mg/day	For less severe bleeding. Often causes nausea and vomiting. Should be followed by conjugated estrogen 1.25 to 2.5 mg plus 10 mg of medroxygesterone per day for abouth 10 days.
Oral conjugated estrogen (Premarin) 2.5 to 5 mg/day	Used for DUB and patients with low-dose OCPs with midcycle spotting.
Conjugated estrogen 1.25 mg/day	Used in treatment of peri- or postmenopausal women.
Conjugated estrogens 0.625 to 1.25 mg Q day plus cyclic medroxyprogesterone 10 mg for 10 to 14 days each month	Mainly used for chronic DUB. Good for patients who desire Effective for long-term use. Much experience with long-term use for other problems. Watch for GI and renal side-effects.
Clomiphene citrate (Clomid, Serophene)	Androgenic side-effects limit use. Acts as anti-estrogen and prevents ovulation.
Progesterone-containing IUD	
NSAIDS Naproxen (Naprosyn) 500 mg BiD, menfenamic acid (Ponstel) 500 mg TiD, ethamsylate 500 mg QiD	Primarily used to thin the endometrium prior to surgery. Used when hormonal methods have failed or are containdicated. May cause ospeporiis the chrnoic use, DUB will also recur in up 10 10:of women treants
Danazol (Danocrine) 200 to 800 mg/day for 3 to 6 months	
GnRH agonists goserelin acetate (Zoladex), 3.6 mg SQ every 28 days; leuprolide acetate (Lupron) or nafarelin acetate (Syneral)	

approximately 85% and is more effective in patents over the age of 35 years. Amenorrhea may occur in 29% of patients. There is some concern that cancers could be missed, since no tissue is available for pathologic study.

Possible risks include fluid overload, endometritis, and uterine perforation. Laser equipment is expensive and requires special safety precautions.

Hysteroscopic transcervical resection of the endometrium (TCRE) makes use of an electrocautery loop or ball to remove or coagulate the endometrium to stop DUB. It may reduce the need for hysterectomy by up to 90%, and has been shown to have a lower overall procedure cost (including retreatment costs and eventual hysterectomies) than immediate hysterectomy for more severe DUB. The goal is to ablate the endometrium and encourage endometrial adhesions resulting in hypo or amenorrhea. The hysteroscope is considerably less expensive to buy and maintain than the laser but carries the risks of fluid overload, endometritis, and uterine perforation. The potential fluid overload problem can be alleviated by the use of carbon-dioxide gas or Dextran 70 solution to distend the uterus. Hysteroscopy is most effective in women who are over the age of 35, and postmenopausal HRT may be safely started or continued in patients after endometrial ablation. There have been 3 reported cases of adenocarcinoma diagnosed after endometrial ablation for DUB.

The enometrium may also be hysteroscopically ablated via the insertion of a thermal uterine balloon. The system consists of a control system attached to a 16cm by 5mm catheter with a latex balloon on the end that houses a heating element. A sterile 5%dextrose solution is instilled until the pressure reaches between 160 and 180mmHg. The solution is heated to 87 degrees C. for 8 minutes and then the device is removed. The treatment has been fount to be as efficatious as roller-ball ablation with less complications.

Hysterectomy remains the most absolutely curative treatment for DUB. Elective hysterectomy has a mortality rate of six per 10,000 operations. One randomized study found that hysterectomy was associated with more morbidity and much longer healing times than endometrial ablation. Fortunately, a recent study found that sexual functioning improved overall after hysterectomy with an increase in sexual activity and a decrease in problems with sexual functioning. It still remains a popular method of treating DUB, especially in industrialized countries.

Ref:

Congratulations !

The Winners of WOMEN'S HEALTH *Quiz Competition* (Vol-3, No.-2, July-Sept 2011)

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