Abbreviations

WOMEN'S HEALTH

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Learning Objectives

1. Design the best contraceptive management plan for a patient after assessing the contraindications, benefits, risks, and therapeutic uses of various contraceptive options and how they relate to patient-specific factors.
2. Apply the information available based on the severity of bleeding for managing dysfunctional uterine bleeding.
3. Demonstrate an understanding of how to treat various menstrual-related disorders, such as premenstrual syndrome, premenstrual dysphoric disorder, and dysmenorrhea.
4. Develop a management plan regarding non-pharmacological and pharmacological therapy for common complaints associated with menopause.
5. Evaluate and incorporate outcome data from prospective, clinical trials on the use of hormones in postmenopausal women into patient-specific education and management plans.

Contraception

Introduction

Contraception is one of the most common health care interventions for women of reproductive age. It has provided couples with several choices about how to prevent pregnancy when desired. Nonetheless, almost 50% of pregnancies that occur annually throughout the world are unintended at the time of conception. In the United States, 66% of births among women 15–19 years of age and 39% of births among women 20–24 years of age are unintended. Why is it that there are such elevated numbers in this modern era? Answers may include lack of access to the health care system, lack of knowledge regarding the various contraceptive options, failure to plan in advance, and user/method failure of the individual contraceptive agents and/or devices.

Commonly used forms of contraception include both nonhormonal and hormonal methods. Nonhormonal methods of contraception include periodic abstinence, barrier methods, spermicides, and the use of the copper intrauterine device (IUD). Although additional nonhormonal methods, such as tubal ligation and vasectomy, also are available, this chapter focuses mainly on the methods that are of most importance to the pharmacist. Hormonal methods include oral, transdermal and vaginal contraceptives, long-acting injectable or implantable methods, and the progestin-releasing IUDs. Because many factors may affect contraceptive failure, it is difficult to determine the actual efficacy of any one contraceptive method; however, estimates of failure rates can be found in Table 1-1. It is important for pharmacists to be familiar with the various available options as well as to understand the contraindications, benefits, risks, and therapeutic use of each of these options to effectively make recommendations to health care providers and counsel patients appropriately.

Nonhormonal Options

Periodic Abstinence

Periodic abstinence, otherwise known as natural family planning or the rhythm method, requires that women do not have sexual intercourse during those times in the menstrual cycle when the chances of getting pregnant are greatest. Patients may be able to determine these fertile times by monitoring changes in cervical discharge, body temperature, cervix position, or in the case of the symptothermal method, a combination of all three. Women may choose this method because they want to avoid drugs and/or devices for medical, philosophical, or religious reasons. Unfortunately, this nonhormonal option has not been highly effective for a variety of reasons, including irregularities in many women's menstrual cycles as well as the difficulty in coping with

Abbreviations

Abbreviations in this Chapter

ACOG	American College of Obstetricians and Gynecologists	IUD	Intrauterine device
CEE	Conjugated equine estrogen	MPA	Medroxyprogesterone acetate
COC	Combined oral contraceptive	NSAID	Nonsteroidal anti-inflammatory drug
DUB	Dysfunctional uterine bleeding	PMS	Premenstrual syndrome
FDA	Food and Drug Administration	STD	Sexually transmitted disease
HERS	Heart and Estrogen/Progestin Replacement Study	WHI	Women's Health Initiative

7–10-day abstinence periods. Periodic abstinence requires much more commitment, discipline, and communication for both the man and the woman than other forms of birth control. In addition, this method obviously does not protect against sexually transmitted diseases (STDs) and, therefore, is not a rational choice for those with multiple sexual partners. Periodic abstinence also is not appropriate for women in which pregnancy would be considered a high medical risk. It is for these reasons that the number of people choosing this method remains small. According to the National Center for Health Statistics in 1995, only 1.5% of women between 15 and 44 years of age reported using periodic abstinence as a means of contraception.

Barrier Methods

Condoms

According to the National Survey of Family Growth in 1995, the male condom comprises about 20% of all contraceptive use. In fact, the use of condoms has continued to increase in the past 10 years, reflecting greater concerns regarding STDs, including human immunodeficiency virus. In addition, condoms are easily accessible, relatively inexpensive ($0.50–0.75 per condom), and fairly simple to use compared to other contraceptive methods. If male condoms are used, those made of latex should be recommended because "natural" condoms (made of lambs' intestines) have not been proven to protect against STDs. For those with a latex allergy, there is a polyurethane condom available in some areas of the United States and research continues in the area of nonlatex condom development. Polyurethane condoms do protect against STDs and human immunodeficiency virus and are resistant to deterioration from storage and lubricants. However, breakage and slippage were 4–6 times greater in randomized, well-designed studies that compared polyurethane condoms with latex condoms. If used correctly (placed over the erect penis before penetration and leaving room at the tip for the ejaculate), the male condom can have high success rates of pregnancy prevention. User failure often arises from delayed placement of the condom or otherwise inappropriate or inconsistent use.

The female condom has been available in Europe since 1992 and is now available in many countries throughout the world. It was approved by the Food and Drug Administration (FDA) in 1993 for marketing and distribution as a single-use product. The female condom is a strong, soft, transparent polyurethane sheath inserted into the vagina before sexual intercourse, providing protection for up to 8 hours. Because part of the condom rests outside the vagina, there is some protection provided to the woman's perineum. It is stronger than latex, has no reported allergic reactions, and, unlike latex, may be used with both oil-based and water-based lubricants. On average, the cost is about $2–3 per condom. As with the male condom, proper instruction on use of the product is vital because user failure may result from improper placement or inconsistent use. The male and female condoms should not be used at the same time, as friction between the two materials could cause product failure.

Diaphragm and Cervical Cap

The diaphragm is a round rubber dome and the cervical cap is a small rubber cup. Both must be prescribed by a health care professional and are to be inserted into the vagina before intercourse to prevent semen from entering a woman's cervix. The diaphragm should be left in place for at least 6 hours and the cervical cap should be left in place for at least 8 hours after intercourse. In fact, the cervical cap can provide protection for up to 48 hours. Some women who are unable to use a diaphragm (those with uterine prolapse or vaginal relaxation) may be able to use the cervical cap. Both are to be used in conjunction with a spermicide to further lower the risk of pregnancy. The cap or diaphragm alone will cost $30–40; however, when the cost of the office visit is factored in, the cost may be as high as $150. Replacement is recommended every 2 years for the diaphragm and annually for the cap. Women allergic to rubber (latex) should avoid the use of diaphragms and cervical caps. Neither product protects against STDs and both have higher failure rates than that of hormonal methods and nonprescription barrier methods, such as condoms. These products are used as a contraceptive method by about 1–2% of women in the United States.

Vaginal Sponge

The vaginal sponge is a donut-shaped polyurethane device containing the spermicide nonoxynol-9. It is inserted into the vagina to cover the cervix and should be left in place for at least 6 hours and up to 24 hours after intercourse. The vaginal sponge is relatively inexpensive (about $2.50 per sponge) and may provide individuals with greater spontaneity of intercourse than other barrier methods. One of the most popular products, the Today Sponge, was voluntarily taken off of the market in 1995 because of manufacturing problems (about 100,000 women were using the product at this time). However, as of 2003,

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Table 1-1. Failure Rates During the First Year of Use, United States

Method	Percent of Women with Pregnancy Lowest Expected/Perfect Use	Typical
No method	85%	85%
Combination pill	0.1	7.6
Progestin-only pill	0.5	3.0
IUDs		
Progesterone IUD	1.5	2.0
Levonorgestrel IUD	0.1	0.1
Copper T 380A	0.6	0.8
Implant	0.05	0.2
Injectable	0.3	3.1
Female sterilization	0.05	0.05
Male sterilization	0.1	0.15
Spermicides	6.0	25.7
Periodic abstinence		20.5
Calendar	9.0	
Ovulation method	3.0	
Symptothermal	2.0	
After ovulation	1.0	
Withdrawal	4.0	23.6
Cervical cap		
Parous women	20.0	40.0
Nulliparous women	9.0	20.0
Sponge		
Parous women	20.0	40.0
Nulliparous women	9.0	20.0
Diaphragm and spermicides	6.0	12.1
Condom		
Male	3.0	13.9
Female	5.0	21.0

IUD = intrauterine device.
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it is available again over-the-counter in the United States. In addition, Lea's Shield is a new product that recently has come to market. This barrier contraceptive fits over the cervix and is designed to remain in place for 48 hours after intercourse. Unfortunately, the vaginal sponge is less effective than prescription methods, including other prescription barrier methods. As with the diaphragm and cervical cap, the vaginal sponge does not protect against STDs. Women with an allergy to nonoxynol-9 should not use the vaginal sponge.

Copper IUD

An IUD is a small, plastic device that is inserted into the uterus to prevent pregnancy. It produces a local inflammatory action, thereby inhibiting the sperm from reaching the egg. The copper IUD (Tcu-380A) has a copper wire coiled around the stem and arms and can be used for up to 10 years. Overall, IUDs are effective and convenient and are used by about 156 million women worldwide. However, in the United States, the number of reproductive age women using the device decreased by 66% from 1982 to 1988, and further decreased in 1995 (from 7.1% to 2% to 0.8%, respectively). This decrease in use is mostly because of public concerns regarding IUD-related infection and many lawsuits that have occurred throughout the years. Although the IUD that was associated with increases in pelvic inflammatory disease (the Dalkon Shield) was taken off of the market more than 25 years ago, the litigation and media coverage that occurred generated fears and misconceptions that continue today. The use of a copper IUD is appropriate for women in stable and monogamous relationships and those who are at low risk of STDs. It is important to make patients aware of the fact that IUDs do not protect against STDs and to recommend a latex condom for protection. Intrauterine devices are not appropriate in the following cases: known or suspected pregnancy, undiagnosed vaginal bleeding, immunosuppression, active genital tract infection or cancer, history of pelvic inflammatory disease, and those at high risk of STDs. Nulliparous women can use an IUD; however, it is more difficult to pass an IUD through a cervix that has not been previously dilated and expulsion rates are higher in this group. The median time to planned pregnancy after removal of an IUD is 3 months. The cost of an IUD varies, depending on the medical visit charge and may range from $150 to $300; however, after the initial insertion, the ongoing costs are minimal.

Spermicides

Spermicides may be used alone or in conjunction with a barrier method of contraception, such as the diaphragm, cervical cap, or condom. The most well-known chemical spermicide is nonoxynol-9 and is used by about 5% of

women in the United States. Spermicides come in many formulations, including gels, creams, foams, suppositories, and dissolvable films. Creams and gels usually come in a tube with a plastic applicator to insert the product into the vagina, foams come in aerosol containers with an applicator and films are paper-thin 2x2-inch sheets that melt when wet and can be folded and placed into the vagina. Nonoxynol-9 is available without a prescription and is relatively inexpensive (patients will pay $0.35 for discount suppositories or gel, or $1.30 for single-use gel packets). Users must make a small initial investment to purchase a container of foam, a package of film, a package of suppositories, or a tube of gel or cream. The World Health Organization along with the Contraceptive Research and Development Program group currently stated that nonoxynol-9 remains a viable contraceptive option for women at low risk of human immunodeficiency virus infection. The group also stated that when used with a barrier method, nonoxynol-9 is more effective than when used alone. On the down side, there is no evidence that condoms lubricated with nonoxynol-9 are any more effective in preventing pregnancy or infection than condoms lubricated with silicone. Women who have multiple daily acts of intercourse or who are otherwise at increased risk of human immunodeficiency virus infection should be advised to choose another method of contraception. The group also stated that nonoxynol-9 should not be used alone for the purpose of STD or human immunodeficiency virus prevention. Instead, condoms should always be used to prevent these infections.

Hormonal Options

Combination Contraceptives

Oral

Oral contraceptives have been available in the United States for more than 4 decades and they still remain the most popular form of reversible contraception. From 1988 to 1995, oral contraceptive use decreased in women younger than 25 years of age and rose among women 30–44 years of age. In part, this decrease in younger women is because of the availability of newer forms of contraception, such as injectable or implantable methods and increased condom use.

Combined oral contraceptives (COCs) contain both an estrogen and a progestin. Ethinyl estradiol is the pharmacologically active estrogen used in COCs (mestranol is converted in vivo to ethinyl estradiol) and the progestin component varies. The progestins currently available in the United States include norethindrone, norethindrone acetate, levonorgestrel, norgestrel, desogestrel, norgestimate, and drospirenone. These progestins typically are categorized into "generations", which basically are differentiated by chemical structure and overall hormonal activity. Progestins vary in their progestational activity and differ with respect to inherent estrogenic and androgenic effects. Norethindrone and norethindrone acetate are considered first-generation progestins; levonorgestrel and norgestrel are considered second-generation progestins; and desogestrel and norgestimate are third-generation progestins. For instance, third-generation progestins appear to be potent progestational agents with little to no estrogenic activity and less androgenic effects compared to levonorgestrel. Drospirenone is a new progestin that has not been categorized in this manner. Combined oral contraceptives prevent pregnancy primarily by suppressing ovulation through the combined actions of both estrogen and progestin. Ethinyl estradiol causes suppression of follicle-stimulating hormone and luteinizing hormone, whereas the progestin component primarily suppresses luteinizing hormone. The progestin also may cause an increase in cervical mucus, hampering the transport of sperm. Ethinyl estradiol confers only estrogenic activity; however, progestins confer progestational activity and also may confer estrogenic and androgenic activity because of their ability to enter cells and bind to specific cytoplasmic receptors. These differences are important to consider when evaluating COCs, each containing different types and amounts of estrogen and progestin, therefore possessing different biologic activity profiles and side effect profiles. For example, if a woman complains of acne, which is primarily because of excess androgen, it would be prudent to switch to a COC with lower androgenic activity. On the other hand, if a woman complains of nausea and vomiting, which is primarily because of excess estrogen, it would be appropriate to recommend a COC with lower estrogenic activity. However, it is important to remember that it is impossible to make a clinically useful interpretation of biologic activity based solely on the amount of estrogen and progestin present. The dose of the individual estrogen and progestin, the activity of the progestin present, and the potentiating and antagonistic effects of one component on the other also must be taken into account. See the Annotated Bibliography for currently available monophasic and multiphasic oral contraceptives and their selected activities.

Advantages of COCs include low "method failure," ease of reversibility, relatively safe side effect profile, and lack of interference with intercourse. Noncontraceptive benefits of COCs include decreases in the risk of endometrial and ovarian cancer (at least a 50% risk reduction in women who have used COCs for 5 years or more), reduction in the risk for benign (fibrocystic) breast disease and of functional ovarian cysts (80–90% reduction because of suppression of follicle-stimulating hormone/luteinizing hormone), reduction in premenstrual symptoms, and reduction in the incidence and severity of some causes of pelvic inflammatory disease. In addition, COCs allow a woman to manipulate the menstrual period to prevent bleeding during weekends, vacations, and special events.

Combined oral contraceptives can be associated with varying side effects and, as previously discussed, are related to the specific estrogenic, progestational, or androgenic activity. The hormonal etiology of COC adverse effects are listed in Table 1-2. Side effects may occur during the first three cycles of COC use, but should decrease in number and severity after that time. Unless accompanied by serious disease or severe discomfort, the initial COC chosen should be continued for 3 months before a change is made to adjust the hormonal content. Symptoms that may be warning signs of serious trouble can be recalled by using the ACHES pneumonic (Abdominal pain, Chest pain, Headache, Eye problems, or Severe leg pain). According to class product labeling, contraindications to the use of COCs include:

Table 1-2. Hormonal Etiology of Common Oral Contraceptive Adverse Effects

Adverse Event	Causal Factors/Comments
Absence of withdrawal menses	Insufficient estrogen to develop endometrium and vessels May appear after OCs taken for several months
Heavy menstruation	Insufficient progestin activity or excess estrogen activity
Breakthrough bleeding and spotting	Early: Insufficient estrogen activity; associated with amenorrhea Late: Insufficient progestin activity Bleeding usually occurs in first cycles of OC use
Headache	Most likely because of estrogen component Associated with fluid retention/vascular spasm
Mood changes (depression)	If associated with lethargy and weakness, may be because of estrogen If characterized by apathy, feelings of dejection, anorexia, insomnia, and restlessness, may be androgen/progestin excess
Nausea and vomiting	Related to estrogen dose Most severe with initial cycles and improves over time
Acne and hair changes	Associated with androgenic activity
Decreased libido	Associated with low androgenic activity
Weight gain	If appetite is increased because of progestin activity If weight gain is cyclic, with bloating and edema, because of estrogen activity

OC = oral contraception.

presence or history of thromboembolic disease, known or suspected pregnancy, cerebral vascular or coronary artery disease, known or suspected breast or endometrial carcinoma or other estrogen-dependent neoplasia, undiagnosed abnormal genital bleeding, hepatic adenomas or carcinomas, and cholestatic jaundice of pregnancy. In addition, COCs should not be used in women older than 35 years of age who smoke (especially 15 or more cigarettes per day) because of the risk of thromboembolism. The controversies lie with the use of COCs in patients with coexisting medical conditions. The authors would refer the reader to the American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin for specific recommendations for COC use in these various medical conditions. Of particular note, a recent study has shown that current or former use of oral contraceptives among women 35–64 years of age does not significantly increase the risk of breast cancer. This was found to be true for women with a family history of the disease as well.

The potential for drug interactions with COCs has always been an issue and continues to raise debate. Regarding women taking antibiotics and COCs, there have been anecdotal reports of failure to prevent pregnancy, reportedly by reducing enterohepatic recycling. The actual incidence of pregnancy in women who take antibiotics while taking birth control is unknown and, in reality, the clinical significance of this interaction is probably minimal. There also is thought that some women may be more susceptible than others to getting pregnant when taking both drugs and that some antibiotics may be more likely to cause a problem. For example, there are pharmacokinetic data demonstrating interactions with enzyme inducers, such as rifampin and griseofulvin; however, with most other antibiotics, the data are anecdotal. Unfortunately, it is impossible to predict which women are at higher risk. Therefore, it is still prudent to counsel women who are taking a COC and require an antibiotic to use backup contraception while taking the antibiotic and for at least 7 days after. It also is best to recommend another form of contraception for women who must continue chronic drugs that may significantly interact with COCs (e.g., enzyme-inducing anticonvulsants). In addition, there are multiple reports of breakthrough bleeding in women concomitantly taking oral contraceptives and St. John's wort. Studies on its ability to induce liver enzymes are inconsistent; however, until more information is available, it would seem prudent to advise women of a possible interaction and suggest that they use an alternative contraceptive method if pregnancy is to be avoided or avoid the use of St. John's wort altogether.

Patients who are starting COCs for the first time should be counseled to take their tablet at the same time each day. There are two options for when to start taking the drug: Sunday start (taking the first active tablet on the Sunday after the period begins and using backup contraception for 7 days after) and day 1 start (taking the first active tablet during the first 24 hours of the period, with no need for backup contraception). Regardless of the method, it is thought to be prudent to counsel women to use a backup method for the entire first month of use—not because the COC takes that long to become effective, but because of user failure within the first month of use. There are recommendations listed in various sources regarding management of missed doses; however, the bottom line is that a backup method is not necessary if only one tablet is missed and the patient takes it as soon as she remembers it. However, if two or more tablets are missed, backup is necessary. In general, when two tablets are missed in week 1 or 2, the patient should be instructed to take two tablets for 2 days and then resume the normal course. When two tablets are missed in week 3 (Sunday starter), the patient

ACOG Committee on Practice Bulletins-Gynecology. ACOG Practice Bulletin. The use of hormonal contraception in women with coexisting medical conditions. Int J Gynaecol Obstet 2001;75:93–106.

Marchbanks PA, McDonald JA, Wilson HG, et al. Oral contraceptives and the risk of breast cancer. N Engl J Med 2002;346:2025–32.

should be instructed to take one tablet every day until Sunday, throw out the rest of the pack and then begin a new pack that same day. When two tablets are missed in week 3 (day 1 starter), the patient should be instructed to throw out the rest of the pack and begin a new pack that same day. If three or more tablets are missed during the first 3 weeks of the pack, instructions are the same as if two tablets are missed in week 3. Patients who continually forget to take their drugs should think about using one of the newer forms of contraception that may improve adherence.

What is new regarding COCs? A new progestin, drospirenone (in the product Yasmin), has become available. Drospirenone is a spironolactone analog that has antimineralocorticoid activity and may help those suffering from bloating and/or weight gain. However, because of its potassium-sparing ability, potassium levels should be monitored at baseline and during the first month. Health care professionals must be careful when using other drugs or supplements that may increase potassium levels. It is important to inform patients that this new oral contraceptive should not be used as a true weight loss agent. The use of lower dose estrogen products also has come to the forefront. Products containing 20 mcg ethinyl estradiol are being used frequently, especially in teenagers and those in the perimenopausal state. In addition, there have been new or improved delivery systems that have become available in the past 2–3 years, such as the transdermal patch or vaginal ring. Ovcon 35 chewable is an oral, spearmint-flavored contraceptive tablet that recently has come to market. It contains the same estrogen and progestin as in ovcon 35 and, if chewed and swallowed, the woman should be instructed to drink a full glass of liquid immediately afterward. The chewable tablet is simply another alternative to the variety of contraceptive options available and its use should be determined by patient preference.

One of the most interesting new concepts has been the idea of lengthening the oral contraceptive cycle (i.e., not menstruating each month). This idea stems from the theory that COCs suppress the release of endogenous estrogen and progesterone, resulting in little build up of the uterine lining compared to no use of COCs. There have been several studies evaluating this concept, even dating back to the 1970s. In two recent trials, women being cycled had fewer symptomatic days overall and spotting days were not significantly different with cycling versus a standard regimen. At this point, it is being mostly studied in women who suffer from severe premenstrual syndrome (PMS). Even though lengthening of the cycle could be done with any of the currently available monophasic COCs, a new product (Seasonale), in which women will menstruate once every 3 months or once a season, has come to market.

Transdermal

The contraceptive patch is a once weekly transdermal matrix-type patch that delivers ethinyl estradiol 20 mcg and norelgestromin 150 mcg/day. It is roughly the size of a half dollar and can be applied to the abdomen, buttocks, upper torso, or upper outer arm (not including breasts). A new patch should be applied weekly for 3 weeks (week 4 is patch-free). If a woman is starting the patch for the first time and applies the patch within 24 hours of the start of her menstrual cycle, no backup contraception is necessary. If it has been more than 24 hours, she should use additional contraception for the next 7 days. Similarly, if a woman is switching from COCs and the patch is not applied on the first day of her menstrual cycle, backup contraception should be used for 7 days. If the patch falls off and it has been less than 24 hours, the patient should be instructed to reapply the patch and no backup contraception is necessary. However, if it has been more than 24 hours or the patient does not know when it fell off, the patient should be instructed to start a brand new cycle and to use backup contraception for the next 7 days. In the case that a patient would forget to change her patch, there is a 48-hour forgiveness period. If it has been more than 48 hours, the patient should be instructed to use backup contraception for 7 days after reapplying the new patch. The obvious advantage of the combination patch is convenience—the fact that women do not have to remember to take a tablet every day. The cost is about $30 per package of three, which is similar to the monthly cost of brand name COCs. The product also is sold as individual patches, for those cases in which the patch falls off and needs to be replaced.

The efficacy of the combination patch is similar to COCs, with a pregnancy rate of 1% (one per 100 women-years of use). Although the patch has shown greater breakthrough bleeding in the first two cycles compared to traditional COCs, this difference did not continue with subsequent cycles and compliance was shown to be significantly better with the patch. Among more than 70,000 patches worn, 4.7% were replaced either because they fell off (1.8%) or became partly detached (2.9%). In a study of 87 patches worn under the conditions of variable temperature, humidity, and physical exertion, fewer than 2% had to be replaced. Of note, the manufacturer does not recommend the patch for women who weigh greater than 90 kg because there was a statistically significant increase in pregnancies in these women (greater than 3% failure rate). Common adverse effects include application site reactions, breast discomfort, headache, and nausea. Application site reactions can be avoided by applying to a new spot on the skin each week (although it can be kept within the same anatomic area). Contraindications are similar to COCs because the patch contains both estrogen and progestin.

Sulak PJ, Kuehl TJ, Ortiz M, Shull BL. Acceptance of altering the standard 21-day/7-day oral contraceptive regimen to delay menses and reduce hormone withdrawal symptoms. Am J Obstet Gynecol 2002;186:1142–9.

Miller L, Notter KM. Menstrual reduction with extended use of combination oral contraceptive pills: randomized controlled trial. Obstet Gynecol 2001;98:771–8.

Audet MC, Moreau M, Koltun WD, et al. Evaluation of contraceptive efficacy and cycle control of a transdermal contraceptive patch vs. an older contraceptive: a randomized controlled trial. JAMA 2001;285:2347–54.

Abrams LS, Skee DM, Natarajan J, et al. Pharmacokinetics of Ortho Evra under conditions of heat, humidity, and exercise. J Clin Pharmacol 2001;41:1301–9.

Vaginal

The contraceptive ring is a flexible, transparent vaginal ring which releases, on average, 120 mcg/day etonogestrel and 15 mcg/day ethinyl estradiol over a 3-week period of use. It should be kept in the refrigerator before dispensing, but can be kept at room temperature for up to 4 months. Women should leave the ring in for 3 weeks and then remove it for week 4 of the cycle. If a woman is starting contraception for the first time, the ring should be inserted on or before day 5 of the cycle. Backup contraception should be used for 7 days after insertion of the ring. For a woman switching from COCs, the vaginal ring can be inserted anytime within 7 days after the last tablet and no later than the day that a new cycle would have been started. No backup contraception is necessary. If the ring is expelled and it has been out for less than 3 hours, it can be washed off with lukewarm water and then reinserted. If it has been greater than 3 hours or if the woman does not know when it was expelled, the ring can be reinserted but the patient must be instructed to use backup contraception for at least 7 days after reinsertion. This particular product is a convenient alternative to COCs and the cost is about $40/month, slightly more than that of other hormonal methods.

Efficacy of the vaginal ring is similar to that of COCs, with a pregnancy rate of 1–2% (1–2 per 100 women-years of use). Despite releasing only 15 mcg ethinyl estradiol/day, cycle control and incidence of irregular withdrawal bleeding does not appear to be compromised. One study showed that the incidence of irregular bleeding was less than 5% in all cycles, which was lower than the COC control group (5.4–38.8%). The incidence of normal, intended bleeding patterns was significantly higher in the group receiving the vaginal ring.

The most common adverse effects reported include vaginitis, headache, upper respiratory tract infections, leukorrhea, sinusitis, weight gain, and nausea. The most common reasons for discontinuation include device-related events, such as foreign body sensation, coital problems, and device expulsion. It is possible that the male partner may actually feel the vaginal ring during intercourse; however, studies have demonstrated that it does not significantly affect overall sexual satisfaction for the male. As with the patch, contraindications are similar to those found with COCs.

Injectable

A monthly intramuscular injection containing both estradiol cypionate and medroxyprogesterone acetate (MPA) has been on the market. The recommended dose is 0.5 ml (estradiol cypionate 5 mg and MPA 25 mg) once per month. It can be injected into the arm, thigh, or buttock. The first injection should be given within the first 5 days of the menstrual cycle and subsequent injections should be given between 28 and 30 days after the previous injection, not to exceed 33 days. If the patient exceeds 33 days, pregnancy should be ruled out before another injection is given. When switching from COCs to this particular injection, patients should be given their first injection within 7 days after taking their last active tablet. In essence, this combination injection is another alternative to COCs in women who do not wish to take a tablet every day. Compared to the MPA injection, this product has a quicker return to fertility (about 2–4 months on average) and causes less weight gain (women gained an average of 4 pounds during the first year and an additional 2 pounds during the second year of use). The injection costs about $35 per dose.

The most frequent adverse reactions leading to discontinuation were weight gain, heavy menstruation, absence of menses, irregular menses, vaginal spotting, mood swings, acne, breast tenderness, headache, painful menstruation, nausea, and depression. Contraindications are similar to those seen with COCs.

Although the prefilled syringes are no longer in production at this time, vials of the drug are still available. However, the use of this particular product has been reduced significantly because of these changes as well as the fact that the original manufacturer was bought out by another company. In essence, the future of this product is in question and its accessibility may be limited.

Progestin-only Contraceptives

Oral

Progestin-only pills or minipills include products that contain 0.35 mg of norethindrone and 0.075 mg of norgestrel. Prevention of pregnancy occurs through inhibiting ovulation, thickening cervical mucus, and altering the endometrium. The minipill may be an appropriate choice in situations where estrogen is contraindicated. In addition, progestin-only pills do exhibit immediate effectiveness (less than 24 hours), have no adverse effects on breastfeeding, and return to fertility is immediate when discontinued. Unfortunately, because of small numbers of users in studies, it is not known if the noncontraceptive benefits associated with COCs apply to the minipill. However, the impact that progestins have on ovulation, cervical mucus, and the endometrium tend to indicate that these benefits would be present.

Even more important with the minipill than with COCs, it must be taken every day at the exact same time. In fact, patients should be counseled to use a backup method of contraception for at least the next 48 hours if they are 3 hours late or more in taking their dose. Failure rates have been documented to range from 1.1 to 9.6 per 100 women in the first year of use, with younger women having the most failures. The most common complaint and cause for discontinuation among women using the minipill is irregular bleeding. The incidence of other minor side effects is low, probably at the same rate that would be encountered with placebo. The bottom line is that, clinically, minipills are not used on a regular basis (less than 1% of all oral contraceptive prescriptions) because of the higher rate of failure and availability of other more reasonable alternatives. This is especially true for unmotivated/disorganized adults or young adolescents.

Bjarnadottir RI, Tuppurainen M, Killick SR. Comparison of cycle control with a combined contraceptive vaginal ring and oral levonorgestrel/ethinyl estradiol. Am J Obstet Gynecol 2002;186:389–95.

Abbreviations

Injectable

The progestin-only injection has been available in the United States since 1992 and represents about 5% of all contraceptive methods used; however, rates of use are continuing to increase with time. Medroxyprogesterone acetate inhibits the secretion of gonadotropins (follicle-stimulating hormone and luteinizing hormone), produces a shallow and atrophic endometrium, and produces thick cervical mucus, all of which contribute to its efficacy. It is a deep intramuscular injection of 150 mg of MPA, which can be injected into the gluteal or deltoid muscle within 5 days after the onset of menstrual bleeding. If the injection is not given within 5 days, a backup contraceptive method should be used for 2 weeks. Even though the injection can inhibit ovulation for up to 13 weeks, the dose should ideally be repeated once every 12 weeks to ensure continuous contraception. Women with a contraindication to the use of estrogen can be given this injection and it is much easier to adhere to than the daily regimen required with the minipill. It also is an acceptable option in breastfeeding women. The MPA injection is highly effective and because serum concentrations are relatively high, it is not influenced by weight or by the use of drugs that stimulate hepatic enzymes. In addition, potential noncontraceptive benefits of this agent include scanty or no menses, decreased incidence of anemia and menstrual cramps/pain, decreased risk of endometrial and ovarian cancer, and decreased risk of pelvic inflammatory disease.

Disadvantages of the progestin-only injection include irregular menstrual bleeding, weight gain, and breast tenderness. Even though the manufacturer lists depression as a side effect, two recent, well-designed studies do not support this; therefore, the diagnosis of depression should not preclude the use of this agent. Up to 25% of patients discontinue this agent in the first year of use because of irregular bleeding; however, this irregularity decreases with time. In fact, after 5 years, 80% of users are amenorrheic. In addition, there has been documentation of up to 5 pounds of weight gain per year of use, which is higher than that documented for other hormonal contraceptives. This is one of the most common reasons that women discontinue the agent. However, as with oral contraceptives, the weight gain may not be hormone-induced as much as it may reflect lifestyle and aging. Relatively few controlled studies have specifically addressed this issue and attempts to confirm this weight gain with the MPA injection have met with conflicting results. Another potential disadvantage is the fact that this particular injectable contraceptive is not readily reversible—it lasts for 3 months regardless of the intervention taken. The delayed return to fertility is 68% at 12 months and 93% at 18 months. Therefore, another form of contraception should be recommended if the woman wants to get pregnant within the next 1–2 years.

One of the most controversial issues associated with the progestin-only injection is the effect that the agent has on bone mineral density. Bone loss has been documented with the use of this agent. However, the degree of bone loss has not been as great as that observed in the early postmenopausal years; furthermore, this amount of loss can be regained. In adults, studies have shown that any degree of bone loss was reversible when the injection was discontinued. More important, patient-oriented outcomes, such as fracture risk, have not been documented with the use of this agent. The World Health Organization states that for adolescents, the progestin-only injection can be used and that the advantages typically outweigh the theoretical or proven risks. However, the organization also states that risk factors for osteoporosis should be assessed and that patients should be educated and encouraged to avoid smoking, optimize calcium/vitamin D intake, and engage in weight-bearing physical activity on a regular basis.

Implantable

The implantable contraceptive, which became available in the United States in 1990, was a device consisting of flexible, hollow silastic (silicone rubber) tubes filled with levonorgestrel. These six matchstick-size tubes were inserted under the skin of the upper arm and were effective for up to 5 years. The tubes slowly delivered 85 mcg/day of levonorgestrel (similar to that of the minipill) during the first 6–12 months of use. This rate would decline gradually to 50 mcg/day by 9 months and 30 mcg/day for the remaining duration of use. The efficacy rate with the implantable contraceptive was high because there was little effort required on the part of the user. As with the minipills and progestin-only injection, women with a contraindication to the use of estrogen could use this system safely. In addition, the implant was obviously convenient, readily reversible, and could be used in breastfeeding women.

Side effects were similar to the minipill and progestin-only injection. The most common side effect was irregular bleeding, which occured in up to 70% of women within the first year. Spotting and bleeding decreased over time and administration of several cycles of a low-dose COC proved helpful. Side effects specific to the levonorgestrel implant included local inflammation or infection at the site and difficulty in removal.

Because of lawsuits associated with the use of the system, mostly related to infection and problems with removal of the rods, the use of the levonorgestrel implant dramatically decreased throughout the 1990s. Many of these problems were misrepresented and exaggerated in the media; however, the public image of the product was ruined. To worsen the problem, the manufacturer issued two letters in 2000 alerting health care providers that there were several lots produced the year before that might have not had enough levonorgestrel for 5 years of protection. This statement was revoked in 2002 after tests proved otherwise; however, this was another strike against the product. The company has since decided to discontinue distribution of this product in the United States. Despite this, a similar system more than likely will become available in the United States within the next few years. For example, a single-rod implant containing etonogestrel that is effective for up to 3 years currently is available in the United Kingdom. In addition, there are other single-rod implant systems being developed in this country. Time will tell whether these new systems will come to market in the United States and, if so, whether they will become widely used.

Hormonal IUDs

Progestin-releasing IUDs work by thickening cervical mucus, thinning the endometrial lining, inhibiting sperm motility and function, and producing a weak foreign-body effect. One such IUD releases 65 mcg of progesterone per day and is effective for up to 1 year of use. A newer available IUD releases 20 mcg/day of levonorgestrel and has a similar, albeit smaller T-shaped design. This particular product provides continuous protection for up to 5 years and is highly effective in preventing pregnancy. Ovulation is rarely suppressed after the first year of use, even in women with amenorrhea. The levonorgestrel IUD has the lowest ectopic pregnancy rates of any IUD. Side effects of hormonal IUDs are similar to those experienced by users of progestin-only oral contraceptives. As previously discussed, IUD use is common in many other countries; however, their use in this country remains extremely low.

Emergency Contraception

Emergency contraception is defined as methods women can use after intercourse to prevent pregnancy. Emergency contraceptives are thought to act by disrupting ovulation, fertilization, and/or implantation. They are not considered abortifacients, as they act before implantation. Efficacy rates are difficult to measure because the risk of pregnancy, even at the most fertile interval of the menstrual cycle, ranges from 10% to 30%. Pregnancy rates after use of emergency contraception ranges from 0.5% to 2.5%.

Table 1-3 lists the currently available emergency contraceptive regimens. The most used method involves taking multiple tablets of a COC within 72 hours of unprotected intercourse (although the sooner, the better), followed by the same number of tablets 12 hours later. For convenience and ease of use, commercially available kits have become available within the past few years. One such kit contains four tablets of 0.25 mg levonorgestrel and 0.05 mg ethinyl estradiol, a patient information book, and a urine pregnancy test. The pregnancy test can be used to verify an existing pregnancy resulting from intercourse that occurred earlier in the current menstrual cycle or the previous cycles. If a positive pregnancy test is confirmed, the patient should not take the tablets within the kit. Patients should be instructed to take two tablets within 72 hours of unprotected intercourse and then the other two tablets 12 hours later. Another available emergency contraceptive product contains two 0.75-mg levonorgestrel tablets only. Patients should be instructed to take one tablet within 72 hours and then one tablet 12 hours later. The progestin-only regimen has been as effective or more effective than the methods using both estrogen and progestin, but without the estrogenic side effects, such as nausea and vomiting. Therefore, the progestin-only regimen is quickly becoming the regimen of choice and is the current recommendation of ACOG. There are conflicting data with the use of danazol, but overall efficacy rates seem to be lower with this agent. Mifepristone (RU-486), an antiprogestin, is 100% effective when given as one dose of 600 mg. The higher efficacy rate seen with this agent is most likely because it inhibits implantation as well as ovulation. However, mifepristone is not currently available as an emergency contraceptive, only for termination of pregnancy.

There is some controversy regarding the use of emergency contraception after 72 hours. It is known that if these agents are used after 72 hours, their efficacy rates drop significantly. However, pregnancy rates are still lower than would be expected if no contraceptive were administered. A better option in this situation may be the use of a copper IUD, which can be used effectively for up to 5–7 days after unprotected intercourse.

Many women are unaware that any of these options exist or have misconceptions regarding their use. Therefore, it is the responsibility of pharmacists and other health care professionals to educate these patients and provide appropriate instructions on their use. Access to emergency

Table 1-3. Emergency Contraception Options

Method	Hormones/Dose[a]	Available Products	Efficacy
High-dose estrogen	Ethinyl estradiol 5 mg/day for 5 days	0.05 mg tablets	75–80%
Yuzpe	Ethinyl estradiol (100 mcg) plus levonorgestrel (0.5 mg) or norgestrel (1 mg); repeat in 12 hours	Preven as well as many prescription COCs	75–80%
Progestin-only	Levonorgestrel 0.75 mg; repeat in 12 hours	Plan B	75–89%
Danazol	Antigonadotropin 400 mg given 3 times, 12 hours apart	200 mg capsules	86%
Mifepristone	Progesterone antagonist 600 mg single dose	Not indicated in United States for emergency contraception	100%
Copper IUD	Inserted within 120 hours of intercourse		> 90%

[a]The first dose should be given within 72 hours of unprotected intercourse.
COC = combined oral contraceptive; IUD = intrauterine device.

contraception is an issue that has caused much discussion among health care professionals. Because emergency contraception needs to be initiated within 72 hours, it would be preferable for pharmacies to be able to dispense these agents to patients without a prescription. Currently, only the states of Alaska, Washington, California, and New Mexico allow pharmacists to prescribe emergency contraception and an overall increase in awareness of emergency contraception has occurred. At the time this chapter was written, the FDA Advisory Committees on Reproductive Health and Nonprescription Drugs had just recommended the switch of the progestin-only emergency contraceptive product to over-the-counter status. However, final approval of the FDA is still pending. If and when this product obtains over-the-counter status in the United States, it will cost about $30, which will discourage women from using it as a regular form of contraception. Information on available products and the nearest clinic where these agents can be obtained can be found at *http://opr.princeton.edu/ec/* and by calling (888) NOT-2-LATE.

Menstrual-related Disorders

Dysfunctional Uterine Bleeding

Introduction

Dysfunctional uterine bleeding (DUB) is abnormal uterine bleeding with or without endometrial hyperplasia that occurs in the absence of pelvic organ disease, a systemic disorder, or pregnancy. Uterine bleeding may be heavy or light, prolonged, frequent, or random. Dysfunctional uterine bleeding occurs most often in perimenarchal adolescent girls and perimenopausal women and most often is related to anovulatory cycles. Anovulation and leiomyomas (benign tumors derived from uterine smooth muscle tissue, also known as a uterine fibroids) frequently occur together and often contribute to the development of abnormal uterine bleeding in 30–50-year-old women. Although DUB may resolve over time as the hypothalamic-pituitary-ovarian axis matures or menopause ensues, frequent and/or heavy uterine bleeding may result in iron deficiency anemia, particularly in adolescents. In severe cases, women require hospitalization for fluid management, transfusion, or intravenous hormone therapy. Endometrial hyperplasia and endometrial carcinoma are a concern for women who experience chronic unopposed estrogenic stimulation as a result of anovulatory cycles.

Pathophysiology

In the first 5 years after menarche, lack of maturity of the hypothalamic-pituitary-ovarian axis results in below normal concentrations of gonadotropins (gonadotropin-releasing hormone, follicle-stimulating hormone, and luteinizing hormone) and ovarian hormones (17 β-estradiol and progesterone). Without sufficient ability to mount an luteinizing hormone surge in response to rising estradiol levels, ovulation often fails to occur or is delayed resulting in an increased cycle length. In normal ovulatory cycles, progesterone production from the corpus luteum converts estrogen-primed proliferative endometrium to secretory endometrium, which sloughs predictably in a cyclic fashion if pregnancy does not occur. The normal menstrual cycle averages 28 days ± 7 days with an average of 4 days duration of menstrual flow and 35–40 ml of blood loss. During prolonged or anovulatory cycles, the ovary produces constant, noncycling estrogen levels that stimulate endometrial growth. Progesterone is not available to prepare the endometrium for implantation and the endometrium does not degenerate and slough as it should when progesterone support declines in a normal ovulatory cycle. Thus, the endometrial stroma becomes deciduous and increasingly edematous with an increased vascularity. Estrogen-related endometrial proliferation without periodic shedding causes the endometrial lining to outgrow its blood supply. Without proper vascular and stromal support, this fragile endometrium is at risk to shed irregularly and unpredictably, leading to erratic bleeding or heavy, prolonged menstruation. In time, menstrual cycles become more predictable and regular in most women, but still may last 21–45 days in the first 3 years after menarche. However, if normal menses had not developed within 4 years of menarche, there appears to be an increased likelihood of an underlying disease process contributing to the bleeding dysfunction.

As women approach menopause, progressive decline in ovarian response to gonadotropins results in intermittent ovulatory failure. Initially, chronic stimulation from unopposed estrogen may lead to episodes of frequent, heavy bleeding through a similar mechanism to DUB in an adolescent. As the ovary continues to decline, the ovarian follicles secrete less estradiol and the mean length of menstrual cycle is shortened. Insufficient endometrial proliferation resulting from fluctuating stimulation by low levels of estrogen may lead to infrequent, light uterine spotting or bleeding. Dysfunctional uterine bleeding resulting from an absence of estrogen decline and excess endometrial proliferation is sometimes referred to as estrogen breakthrough bleeding, whereas DUB from declining estrogen and insufficient endometrial proliferation is estrogen withdrawal bleeding. Ovulatory DUB is less common than anovulatory DUB and the bleeding, though abnormally heavy, can be regular. Ovulatory DUB may be due to abnormalities in the luteal phase (after ovulation) of the menstrual cycle or as a result of elevated progesterone-estrogen ratio (i.e., progesterone-only contraceptives) causing an atrophic endometrium, which without sufficient estrogen priming tends to slough.

Diagnosis

Dysfunctional uterine bleeding is a diagnosis of exclusion. Heavy but regular bleeding implies ovulation and is not usually DUB. A woman who bleeds for longer than a week, bleeds more than every 3 weeks, bleeds between menses, or bleeds excessively should be advised to seek medical evaluation for DUB. Heavy menstrual bleeding can be defined as a blood loss of 80 ml or more per menstrual cycle, but this is difficult to quantify objectively and medical care often is sought based on perception of heavy bleeding or altered quality of life. Reproductive tract anomalies, trauma, infections, systemic illnesses, complications of pregnancy, and disorders of coagulation must be ruled out. Evaluation of lifestyle can reveal triggers

of anovulation, such as weight loss, eating disorders, high stress, substance abuse, and excessive exercise. Common hormonal causes of bleeding include hormonal contraception or hormone therapy used by postmenopausal women. It also is important to consider other agents known to affect estrogen metabolism or neurotransmitters (e.g., tobacco smoking, substances of abuse, and psychotropic drugs); herbal therapies that may possess embryotoxic, steroidal, or anticoagulant activity; and agents known to affect coagulation (e.g., warfarin, nonsteroidal anti-inflammatory drugs [NSAIDs], and aspirin).

In addition to a complete medical history (including sexual and family history) and physical examination, a detailed month-by-month account of menstrual periods is necessary. Quantity of flow is subjective and details, such as the number of overflow pads during daily activities or at night, the need to wear multiple pads, number of hours each pad is worn, and type of pad may be more helpful. At minimum, a pregnancy test and a complete blood cell count with a differential and a platelet count should be included. Papanicolaou smear, endometrial sampling, thyroid functions and prolactin, liver functions, and other hormone assays are routine. Because underlying hematologic abnormalities account for a significant percentage (almost 20% in a 9-year case review) of adolescents with severe anemia associated with abnormal bleeding, coagulation studies may be especially appropriate in this population. Women who should be evaluated for endometrial carcinoma include those who are at high risk because of age (older than 35 years), morbid obesity, diabetes or chronic hypertension, or longstanding, chronic eugonadal anovulation. Other laboratory and diagnostic evaluations should be based on initial medical and history findings.

Treatment

Dysfunctional uterine bleeding often requires medical or surgical treatment because it can cause significant uterine blood loss resulting in iron deficiency anemia and overstimulation of endometrial growth, which may increase the risk of endometrial cancer. Management goals for women with DUB are to establish the cause (estrogen breakthrough vs. estrogen withdrawal, iatrogenic), treat any pathology present, prevent cancer, and to control and prevent abnormal bleeding. Although there is an overall lack of consensus regarding the management of DUB, immediate treatment strategies can be categorized based on the severity of bleeding (Table 1-4).

Hormone therapy is the most effective medical therapy for acute bleeding, but at times, it may seem incongruous with the pathophysiology. For example, women with severe, heavy bleeding initially require high-dose estrogen therapy to repair a raw, denuded endometrium that resulted from prolonged, but unopposed, estrogen exposure. Although the exact mechanism is debatable, estrogen is thought to exert an early-onset capillary hemostasis by increasing the production of fibrinogen, factor IV, and factor X in blood, as well as by increasing platelet aggregation and decreasing capillary permeability. Continued high-dose estrogen allows proliferation of denuded areas of endometrium and induces formation of progesterone receptors. This enhances the efficacy of subsequent progestin treatment that is necessary to produce a synchronized and controlled uterine bleeding that more resembles a normal cycle.

Once the acute situation is under control, long-term therapeutic decisions will be influenced by the patient's age, past history, social and financial considerations, fertility status, and opinion of acceptable bleeding patterns. In women of childbearing age, therapy should allow predictable, manageable menstrual cycles or induce ovulation in patients who desire pregnancy. In older women who may be approaching menopause, treatment may help to offset symptoms. Women whose symptoms are severe and resistant to medical therapy may choose surgical treatments, including dilation and curettage, endometrial ablation, or hysterectomy (definitive treatment for DUB).

Severe Bleeding

Emergent DUB with prolonged, heavy bleeding and anemia (hemoglobin less than 9 g/dl) or hypovolemia often requires hospitalization and usually can be controlled with a conjugated equine estrogen (CEE) in doses of 25 mg intravenously every 4 hours for 12–24 hours. Flow should abate within 24 hours. If bleeding is still present after 48 hours, surgical management should be considered. Once bleeding has stopped, treatment may be shifted to high-dose oral estrogen for, typically, a total of 21 days. Numerous regimens are in use and none is more effective than another. Typical regimens are listed below.

- CEE orally 2.5 mg 4 times/day for 21 days
- CEE orally 1.25 mg every 4 hours for 24 hours; then daily doses of 1.25–2.5 mg for total of 21 days
- Estradiol orally 2 mg every 4 hours for 24 hours; then daily dose for 21 days
- Monophasic oral contraceptive: accelerated dosing (Table 1-5)

Antiemetics may be needed to manage nausea and vomiting associated with high-dose estrogen. With the exception of a COC, which contains a progestin, the regimens listed here should be followed by progestin to induce a "normal" withdrawal bleed. The most commonly used progestin is MPA added to the past 5–10 days of estrogen therapy, with optimal endometrial transformation occurring at the 10-mg/10-day regimen. Withdrawal bleeding usually occurs within 3–7 days after stopping the progestin. Patients should be told that the withdrawal bleed may be heavy, but it will be limited to a few days and will then stop. On day 5 of withdrawal bleeding, start normal dosing of a low-dose monophasic oral contraceptive cyclically for 3–6 months, then reassess. Oral contraceptives suppress endometrial development, reestablish predictable bleeding patterns, decrease menstrual flow, and lower the risk of iron deficiency anemia.

In women with DUB from prolonged unopposed estrogen production, a few months of oral cyclic progestin for 5–10 days a month begun on the calculated 16th or 21st day of the menstrual cycle may be considered to prevent the actions of unopposed estrogen and stabilize the endometrium. The recommended dose of oral MPA is 5–10 mg/day for 5–10 days. Women with endometrial hyperplasia typically receive longer courses (12–14 days).

Table 1-4. Hormonal Management of Dysfunctional Uterine Bleeding

Bleeding	Recommendations/Other Considerations
Mild Bleeding	
Menses mildly prolonged or irregular, no evidence of anemia	
Nonhormonal therapy is acceptable; possible use of COCs for cycle control	Reassurance Menstrual diary Iron supplementation Nonsteroidal anti-inflammatory drugs
Moderate Bleeding	
Menses prolonged, heavy, or interfering with daily activities; menses interval shortened; mild anemia	
Acute Management	
CEE 2.5 mg orally every day 21–25 days, followed with progestin (MPA 10 mg or norethindrone acetate 5 mg) added to last 5–10 days of estrogen therapy OR Low-dose COCs in accelerated dosing (see Table 1-5)	Initial trial of cyclic progestin therapy is sometimes tried in women thought to have DUB as a result of estrogen breakthrough bleeding
Maintenance	
Low-dose COCs for 3–6 months after bleeding is controlled	Bleeding usually reduced or controlled within first 24 hours
Follow-up	
Reevaluate in 3–6 cycles, then: If birth control desired, continue with COC or levonorgestrel intrauterine system OR Cyclic oral progestin[a] for 5–12 days each month	Consider iron supplementation
Severe Bleeding	
Prolonged, heavy bleeding with anemia, hemoglobin less han 9 g/dl, hypovolemia	
High-dose estrogens (CEE 25 mg IV every 4 hours for 12–48 hours)	Stabilize with IV fluids Blood products, as necessary If no response within 24 hours, consider D&C plus hysterectomy
Follow with high-dose oral estrogen CEE 2.5 mg 4 times/day for 21 days CEE 1.25 mg every 4 hours for 24 hours; then daily doses of 1.25–2.5 mg for total of 21 days Estradiol 2 mg every 4 hours for 24 hours; then daily dose for a total of 21 days Monophasic COC: accelerated dosing (see Table 1-5)	Evaluate for underlying disease Antinauseant may be necessary
With progestin therapy on last 7–10 days of estrogen therapy	
Medroxyprogesterone acetate 5–10 mg every day Norethindrone acetate 5–20 mg every day	Desmopressin has been used to control bleeding when associated with diagnosed bleeding disorders that do not respond entirely to traditional management

[a]Cyclic progestin.
Medroxyprogesterone acetate: 5–10 mg orally every day for 5–12 days every month.
Norethindrone acetate: 5–20 mg orally every day for 5–12 days every month.
CEE = conjugated equine estrogen; COC = combined oral contraceptive; D&C = dilation and curettage; DUB = dysfunctional uterine bleeding; IV = intravenous; MPA = medroxyprogesterone acetate.

The optimal dose and duration of norethindrone acetate therapy is unclear, but doses have ranged from 5 mg/day to 20 mg/day.

Another long-term option for controlling blood loss is the levonorgestrel intrauterine system, which contains a low dose of a progestin that acts locally to suppress endometrial activity. It reduced menstrual blood loss by 94% after 3 months and may be a good option for women desiring long-term contraception. However, irregular vaginal bleeding or spotting is common, especially during the first few months of use. Other side effects include weight gain, breast tenderness, and bloating, and a high incidence of ovarian cysts (see the Contraception section for other considerations).

Hormone suppression with a synthetic estrogen antagonist (danocrine) or gonadotropin-releasing hormone analogs (leuprolide acetate, nafarelin acetate, and goserelin acetate) with add-back estrogen therapy have been used short term (3–6 months) to shrink the endometrium and reduce blood loss in women with DUB. However, these drugs have relatively high prevalence and severity of side effects (weight gain, headache, nausea, tiredness, menopausal symptoms, bone density loss, and acne) and blood loss returns to pretreatment levels after a few cycles. If danocrine is used, barrier contraception is recommended to prevent possible fetal damage.

Iron supplementation should be given to correct anemia. Patients with bleeding disorders may need adjunctive therapy, such as desmopressin acetate or antifibrinolytics (aminocaproic acid and tranexamic acid). An increased concentration of plasminogen activators have been found in the endometrium of women with heavy menstrual bleeding compared to those with normal menstrual loss. Antifibrinolytic drugs, which inhibit plasminogen activators, reduce bleeding by about 40–50%, but typically do not alleviate menstrual cramping. They are taken only during menstruation and can cause headaches, abdominal pain, nausea, and diarrhea, which may limit their usefulness.

Nonsteroidal anti-inflammatory drugs, by providing a balance between thromboxane A_2 (potent vasoconstrictor) and epoprostenol (vasodilator), help reduce blood loss. Naproxen sodium and mefenamic acid are associated with a 46% and 47% decrease in blood loss at the time of menses, respectively. Nonsteroidal anti-inflammatory drugs also relieve menstrual cramps and should be started at the onset of the menstrual flow and continued through the heavy days of bleeding.

Moderate Bleeding

If the bleeding is not associated with severe symptoms, but is interfering with daily activities, or if mild anemia is present, then hormonal treatment is indicated for cycle control and to minimize blood loss. If the bleeding has been prolonged, the endometrium may be raw and denuded in portions. High-dose oral estrogen (oral CEE 2.5 mg for 21–25 days followed by 10 mg MPA for the last 7 days) or accelerated dosing of oral contraceptives is appropriate. For subsequent cycle control, cyclic oral MPA or norethindrone acetate may be prescribed for 5–10 days each month. This regimen may be a helpful stopgap in the perimenarchal adolescent, but is associated with unwanted side effects, such as bloating, increased acne, and increased appetite; does not offer protection against pregnancy; and requires intermittent monthly compliance. Low-dose COCs are effective in improving abnormal bleeding patterns, with 80% of women showing improvement in one study. Treatment for 3–6 months is recommended in those not needing contraception.

Table 1-5. Monophasic Low-dose COC-accelerated Dosing Options

Option 1
One tablet 4 times/day for 2 days, then one tablet 3 times/day for 2 days, then one tablet 2 times/day for 2 days, then one tablet 1 time/day for 2 weeks, then allow withdrawal bleeding
Option 2
One tablet every 4–6 hours until bleeding abates (24 hours), then one tablet once a day to complete 21 days, then allow withdrawal bleeding
Option 3
One tablet every 4–6 hours until bleeding abates (24 hours), then one tablet 2 times/day to complete 7 days, then allow withdrawal bleeding

COC = combined oral contraceptive

Mild Bleeding

Abnormal and irregular bleeding is extremely common in the adolescents and can be considered part of normal reproductive development. Perimenopausal women may begin experiencing prolonged or irregular cycles up to 10 years before menopause. Reassurance and education about the normal variations in the menstrual cycle is sufficient for many adolescents and perimenopausal women with mild symptoms of menstrual irregularity or prolonged menses and no evidence of anemia. However, adolescents must be reminded that pregnancy is still possible, even though the cycles are not regular.

Encourage patients to keep a daily menstrual calendar to document severity of blood loss and impact on daily activities. Visualization of cyclic changes also helps to determine cyclic activity and improvement or deterioration over time. In perimenarchal and perimenopausal patients who do not smoke or have other contraindications, low-dose oral contraceptives are an acceptable measure to control irregular cycles even if blood loss is not a major concern. If blood loss is noteworthy, iron supplementation may be worth considering if hormonal therapy is declined.

Davis A, Godwin A, Lippman J, et al. Triphasic norgestimate-ethinyl estradiol for treating dysfunctional uterine bleeding. Obstet Gynecol 2000;96(6):913–20

Abbreviations

Premenstrual Syndrome/Premenstrual Dysphoric Disorder

Introduction

The term "premenstrual syndrome" refers to a cluster of physical and cognitive symptoms that occur during the luteal or secretory phase of the menstrual cycle and subside with the onset of menses. Although up to 80% of menstruating women complain of one or more symptom of PMS, about 40% of women experience symptoms sufficient enough to affect their daily lives and about 2.5–5% experience severe impairment. A variant of PMS that entails more severe psychological symptoms recently has been termed "premenstrual dysphoric disorder".

Etiology

Although the exact cause of PMS is still not completely understood, possible influences include hormonal imbalance (specifically, a low progesterone level during the luteal phase), abnormal neurotransmitter response (specifically changes in the level of serotonin), abnormal hypothalamic-pituitary-adrenal axis function, nutritional deficiency (including magnesium and calcium), and environmental factors (including stress). Because the disorder is likely multifactorial in origin, it may be difficult to determine the best treatment strategy for a particular patient.

Characteristics

Symptoms of PMS vary among individuals; however, common emotional and behavioral symptoms include sadness, anxiety, irritability, fatigue, decreased concentration, and food cravings. Physical signs may include abdominal cramps, bloating, headaches, and breast tenderness. According to ACOG, PMS can be diagnosed if a patient has at least one emotional and one physical symptom during the 5 days before menses and for three consecutive menstrual cycles. Emotional symptoms may consist of depression, angry outbursts, irritability, anxiety, confusion, or social withdrawal. Physical symptoms may consist of breast tenderness, abdominal bloating, headache, or swelling of extremities. The ACOG recommends that a diagnosis be based on diaries kept by women charting their symptoms, preferably for 2–3 consecutive months. The diagnosis of premenstrual dysphoric disorder requires at least a 30% increase in symptom severity from the follicular to luteal phase. At least five symptoms must occur premenstrually, including one of the following: depressed mood or hopelessness, tension or anxiety, affective lability, or irritability. In addition, a woman must experience any combination of the following: decreased interest in activities, difficulty concentrating, lack of energy, change in appetite, change in sleep, feeling out of control or overwhelmed, or other physical symptoms, such as breast tenderness or bloating. These symptoms must be severe enough to interfere with daily activities.

Management

The authors would refer the reader to the ACOG Recommendations for Diagnosis and Treatment of PMS for specific management considerations. As a general rule, step one involves supportive therapy; a complex carbohydrate diet; aerobic exercise; and nutritional supplements, such as calcium, magnesium, and vitamin E and possibly spironolactone. Step two consists of the use of selective serotonin reuptake inhibitors and, if necessary, anxiolytics. Step three includes hormonal ovulation suppression with the use of COCs or gonadotropin-releasing hormone agonists.

Supportive Therapy

Reassurance and counseling have not been studied extensively, but women have anecdotally reported relief when informed that the disorder is fairly common and has a physiologic basis. Mind and body approaches may include such interventions as psychotherapy, relaxation techniques/training, massage, hypnotherapy, biofeedback, guided imagery, and yoga. The best evidence to date is that of relaxation therapy. In a few small trials, progressive muscle relaxation significantly improved the physical symptoms of PMS in women with the most severe baseline symptoms. In addition, ear, hand, and foot reflexology is efficacious at decreasing symptoms of PMS.

Aerobic Exercise

In epidemiological studies, exercise (especially aerobic) has been found to be associated with fewer reports of PMS symptoms and often is overlooked in the practice of conventional medicine. Small prospective studies have confirmed the benefit of moderate aerobic exercise compared to nonaerobic exercise. Even though the data are limited, aerobic exercise should be recommended to all women with PMS because of its various other health benefits.

Dietary Supplementation

There have been 13 randomized, controlled trials evaluating various treatments of dietary nature. Most of these trials had small numbers of patients and focused on magnesium and calcium, which have both been modestly effective in treating PMS. According to ACOG, calcium supplementation (1200–1600 mg elemental calcium) should be considered for those who experience PMS. In addition, small trials have concluded that magnesium at a dose of 200–400 mg/day is effective for the pain associated with PMS. Minimal data are available on the effectiveness of vitamin E; however, data suggest that using 400 IU/day improves affective and somatic symptoms significantly. Even though the effectiveness of vitamin E is most likely minimal, it has no serious side effects and may be useful for its antioxidant properties as well. There is no evidence of clinical benefit from other dietary supplements and they are not recommended for treating PMS at this time. Although vitamin B_6 has been touted as effective, its use should be discouraged because high doses taken for prolonged time periods can cause neurological symptoms.

Complex carbohydrates have been theorized to improve mood and reduce food cravings, probably by increasing levels of tryptophan, the precursor to serotonin. However, definitive answers await the completion of well-designed studies before this can be formally recommended.

Selective Serotonin Reuptake Inhibitors

Selective serotonin reuptake inhibitors are considered first-line agents for treating PMS pharmacologically. This is partly because PMS shares many of the features of depression and anxiety states that have been linked to serotonergic dysregulation and there is increasing evidence that serotonin also may be important in the pathogenesis of premenstrual dysphoria. Fluoxetine has been the most extensively studied of the selective serotonin reuptake inhibitors. Premenstrual symptoms of tension, irritability, and dysphoria are significantly improved with a dose of 20 mg/day. Higher doses show similar benefit but produce more side effects. Fluoxetine is available in 7-day blister packs containing either 10-mg or 20-mg capsules for premenstrual dysphoric disorder. The recommended starting dose is 20 mg every day, with a maximum of 80 mg. Intermittent therapy with selective serotonin reuptake inhibitors (i.e., giving the drug only during the luteal phase [days 15–28] of the cycle), may be as effective as continuous dosing. With this form of dosing, side effects and cost decrease and compliance improves. Other selective serotonin reuptake inhibitors that have beneficial effects similar to fluoxetine include paroxetine, sertraline, citalopram, and fluvoxamine. Antidepressants, such as venlafaxine, nefazodone, and clomipramine, also have data showing decreased PMS symptoms; although it seems that those drugs with primary effects on serotonin are most beneficial, especially in premenstrual dysphoric disorder.

Spironolactone

Because fluid retention is common in the luteal phase, diuretics have been advocated as a potential treatment option. Although many diuretics, including hydrochlorothiazide, metolazone, and triamterene, have been used to treat fluid retention, there is limited evidence that these drugs are truly effective. However, spironolactone, an aldosterone antagonist with antiandrogenic properties, was beneficial in several older randomized, double-blind, placebo-controlled trials. Significant reductions in both somatic and affective complaints have been demonstrated with the use of 100 mg/day. It is thought that spironolactone's antiandrogen effect may provide an added mechanism for reducing symptoms, which may account for its beneficial effects compared to other diuretics. It is recommended that women use 100 mg/day for the 2 weeks before menses to achieve optimal relief of symptoms.

Anxiolytics

Today, the use of selective serotonin reuptake inhibitors has mostly replaced anxiolytics, such as benzodiazepines. Although benzodiazepines have the advantage of working quickly to reduce anxiety and promote sleep, they also have the disadvantage of causing cognitive impairment and the potential for tolerance or dependence on the drug. Therefore, these drugs should only be used short-term in the rare situation in which agitation and anxiety are the primary symptoms of PMS or in those who have found no relief with other treatment options. In addition, benzodiazepines should always be avoided in patients with a history of dependent behavior. Alprazolam, at variable doses and dosing regimens, has been the most widely studied of the benzodiazepines.

Combined Oral Contraceptives

Oral contraceptives have been widely used to treat PMS; however, the current evidence suggests that these agents are most useful when symptoms are primarily physical. If mood symptoms are involved, these agents are less likely to be effective. Multiphasic COCs have been used in PMS, but monophasic COCs tend to cause fewer mood swings and are easier to manage. If COCs are used, patients need to understand that they may experience breast tenderness, nausea/vomiting, mood changes, and other side effects for the first few months of use. Because patients often mistake these symptoms for those of PMS itself, it may be difficult to convince women to continue initial treatment.

Gonadotropin-releasing Hormone Agonists

Gonadotropin-releasing hormone agonists, such as leuprolide and goserelin, are effective in reducing physical and emotional symptoms of PMS. However, the side effects and cost of therapy limit their use and these agents typically are limited to severe cases of PMS, unresponsive to all other treatments. A major concern of continued use of this therapy is the potential for bone loss, which occurs because of the "chemical menopause" that is produced by the gonadotropin-releasing hormone agonist. Often, "add-back" estrogen therapy is needed, which can then actually worsen PMS symptoms. It has been suggested that if estrogen therapy results in a return of symptoms, a bisphosphonate, such as alendronate should be considered for osteoporosis prevention. These women also should be counseled to increase their calcium and vitamin D intake as well as their amount of aerobic exercise.

Dysmenorrhea

Introduction

Primary dysmenorrhea, defined as cramping pain in the lower abdomen at the onset of menses, is the most common menstrual problem in young women. In fact, reported prevalence has been as high as 90%. Severe cramping, leading to missed work or school days each month, may occur in up to 10% of women. It is estimated that this condition costs society about $2 billion annually, largely as a result of lost time from work. Secondary dysmenorrhea, which is not discussed in detail in this chapter, refers to painful menses as a result of pelvic pathology, such as endometriosis, fibroids, or pelvic inflammatory disease.

Etiology

Although the etiology of primary dysmenorrhea is not fully understood, it is thought that the action of uterine prostaglandins plays a significant role. As the endometrial lining sheds, the endometrial cells release prostaglandin $F_{2\alpha}$, which in turn stimulates myometrial contractions, ischemia, and sensitization of nerve endings. Studies have shown that women with the most severe cramping have higher levels of prostaglandin $F_{2\alpha}$, which provide clinical evidence for this theory. In addition, the levels of prostaglandin $F_{2\alpha}$, are highest during the first 2 days of menses, when the majority of women complain of symptoms.

Characteristics

Primary dysmenorrhea typically presents during adolescence, with individuals experiencing sharp, intermittent pain in the suprapubic area. This pain can radiate to the lower back and legs and is most prevalent during the first 2 days of menses. Diagnosing primary dysmenorrhea is much less complex than diagnosing PMS and includes a physical examination and patient history. The physical examination should be normal and the patient history should reveal the typical cramping pain associated with the onset of menses. Although PMS is associated with abdominal bloating, breast tenderness, and emotional symptoms, dysmenorrhea typically is limited to lower abdominal cramping pain.

Treatment

Nonsteroidal Anti-Inflammatory Drugs

For most patients, NSAIDs are adequate for controlling mild to moderate cramping and they are the best first-line choice for treatment. These drugs alleviate the pain associated with dysmenorrhea by inhibiting the production and release of prostaglandins. For maximal effectiveness, these drugs should be started immediately after the onset of menstrual flow and should be continued for 48–72 hours. Obviously, there are numerous NSAIDs to choose from; however, no one drug has consistently been more effective than another. Ibuprofen is the most commonly used NSAID, with recommended dosages of 400–600 mg every 4–6 hours; however, naproxen, ketoprofen, and mefenamic acid also are safe and effective. Indomethacin, phenylbutazone, oxyphenylbutazone, and ketorolac, have side effects that limit their use and these drugs should be avoided if possible. Women with a history of peptic ulcer disease, clotting disorder, aspirin-induced asthma, and renal or liver dysfunction should avoid the use of any NSAID. Although NSAIDs are widely available and effective, many women do not use the appropriate dose for an adequate length of time. It is important to try one NSAID for one to two cycles and if there is a poor response, a trial with another NSAID can be attempted. If there is poor response to two different NSAIDs, then oral contraceptives or an alternative treatment should be considered.

Oral Contraceptives

Unless birth control is desired, COCs typically are considered a second-line treatment option. Oral contraceptives must be taken every day to prevent 1–3 days of symptoms per month, whereas NSAIDs only need to be taken for a few days per month. Oral contraceptives work by reducing menstrual fluid volume and by suppressing ovulation. These agents are highly effective, alleviating pain in up to 90% of women. As with NSAIDs, no one oral contraceptive is more beneficial than another. Studies have failed to show a significant difference between monophasic and multiphasic oral contraceptives or among various types of agents within each class. Contraindications, side effects, and benefits of COCs are discussed in more detail in the Hormonal Contraception section. Patients should be instructed to complete three cycles of use before determining usefulness of the COC. If an adequate trial fails to improve symptoms, then the addition of a NSAID or the use of an alternative treatment may be necessary. It is thought that other hormonal contraceptive agents that suppress ovulation also would improve symptoms of dysmenorrhea; however, there is little evidence of benefit for these other agents.

Alternative Therapies

About 10% of women do not respond to NSAIDs, COCs, or a combination of the two treatments. In addition, there may be women who have contraindications to these classes of drugs. For women in whom a secondary cause has been ruled out, there are several alternative treatments that may be tried. These treatments include aerobic exercise; acupuncture; transcutaneous electrical nerve stimulation; psychotherapy; biofeedback; and nutritional supplements, such as omega-3 fatty acids, thiamine, and magnesium. Although all of these treatments have demonstrated some improvement in symptoms in various studies, the number of patients within these studies was small and the patients were followed for short time periods. However, because women may be using these agents on their own, it is important for health care providers to at least be familiar with these therapies and be able to counsel patients effectively on their use. As with PMS, it is thought that these alternative therapies are probably most useful as adjuncts to pharmacological modalities, especially in cases of moderate to severe dysmenorrhea.

Menopausal-related Disorders

Introduction

Menopause is defined as the permanent cessation of menses after the loss of ovarian follicular activity. By definition, this typically occurs after 12 consecutive months of amenorrhea. The median age of onset of menopause is 51. However, the majority of women do not move from a time of regular menses to an abrupt cessation of menses. Rather, they experience perimenopause, a time of menstrual irregularity and declining ovarian function. Throughout perimenopause and menopause, women may suffer from vasomotor symptoms, mood changes, atrophic vaginitis, and genitourinary symptoms as well as such long-term complications as osteoporosis and cardiovascular disease. These last two problems are not discussed in detail in this chapter as they are more specifically addressed in other chapters and books.

Vasomotor Symptoms

Introduction

Vasomotor symptoms, such as hot flashes and sleep disturbances, are the most common problem for women in perimenopause and menopause. Up to 85% of women suffer from vasomotor symptoms to some degree. These women often seek medical attention because of the effect on their overall quality of life. For example, hot flashes and sleep disruption can cause fatigue, poor concentration, and a diminished sense of well-being. In addition, hot flashes can be associated with palpitations and feelings of anxiety,

which may trigger panic attacks in some women. Without treatment, hot flashes typically disappear within 1–2 years; however, for some women, resolution of hot flashes may take longer or may recur after treatment is discontinued.

Etiology

Vasomotor symptoms are thought to be because of a combination of hormonal, metabolic, and psychogenic factors. The majority of these symptoms are the result of the overall loss of ovarian follicular activity and, thus, the decrease in circulating estrogen levels. Follicle-stimulating hormone levels are elevated during this time, signaling the decline in ovarian function. Because estrogen is thought to modulate the firing rate of thermosensitive neurons in the hypothalamus as well as enhance α_2-adrenergic activity, the decline in this hormone leads to hot flashes.

Management

Non-pharmacological Therapy

There are many non-pharmacological treatment options that may be tried before initiating drug therapy. In fact, many women may have already attempted to use these techniques before complaining to their health care provider. These techniques may include relaxation and stress reduction methods, using cold fans/lowering the temperature in the home, drinking cold water, and dressing in layers. In addition, decreasing the use of tobacco and/or alcohol also may help to alleviate hot flashes.

Hormone Therapy

Hormone therapy remains the standard of care for treating vasomotor symptoms. Because recent studies (which is discussed in detail in the Hormone Therapy: Risks and Benefits section) have concluded no benefit from long-term use of hormone therapy, there has been increased interest in the use of nonhormonal treatments for vasomotor symptoms. However, based on the length of these recent studies, short-term use of hormones for hot flashes is most likely safe as well as effective. In a woman with an intact uterus, hormone therapy must include an estrogen and a progestin because the use of estrogen alone can produce endometrial hyperplasia and/or carcinoma. In the absence of a uterus, a progestational agent is unnecessary. There are a variety of hormone therapy options; however, for vasomotor symptoms, the oral and transdermal routes are the most effective. Although recommended doses can be found in Table 1-6, the estrogen dose used to initiate hormone therapy should be individualized because it is strongly dependent on the age of the patient and various other factors.

Women who should not be given hormone therapy include those with a history of documented thrombophlebitis or thromboembolic disorders, breast cancer or other estrogen-dependent neoplasia, and undiagnosed genital bleeding. In addition, estrogen should not be used to prevent or treat cardiovascular disease.

For women who suffer from decreased libido in addition to hot flashes, a product containing testosterone, such as Estratest, can be used. According to the American Association of Clinical Endocrinologists, four groups of women are considered candidates for estrogen plus androgen therapy: women who have had their ovaries removed, those who have not experienced relief of vasomotor symptoms with a maximally tolerable dose of estrogen, those at risk for osteoporosis in whom other modalities are not satisfactory or suitable, and those with unsatisfactory sexual function, especially loss of libido.

Low-dose oral contraceptives are widely used in perimenopausal women to regulate menses as well as provide contraception. When the perimenopausal woman transitions to menopause, hormone therapy may be initiated. Switching from oral contraceptives to hormone therapy can pose a challenge for the patient and the health care provider; however, follicle-stimulating hormone levels (on the last day of the placebo week) can help determine the best time to transition. When follicle-stimulating hormone levels exceed 30 mIU/ml, the switch can be made. Again, the timing of this change often is difficult and variable, depending on the individual woman, and the initiation of hormone therapy often is arbitrary in the clinical setting.

Nonhormonal Therapies

Table 1-7 lists common nonhormonal therapies for treating vasomotor symptoms. Overall, trials with these agents have been short and have involved small numbers of patients. In addition, a disproportionately high number of studies have been completed in women with a history of breast cancer. A strong placebo effect also has been noted in these studies. Whether the results seen in these trials can or should be extrapolated to all postmenopausal women with vasomotor symptoms is still controversial. The strongest evidence of efficacy is that with clonidine and the selective serotonin reuptake inhibitors. Clonidine reduced the frequency of hot flashes and may produce an improvement in overall quality of life. Fluoxetine and venlafaxine were effective in individual controlled trials. A preliminary trial of paroxetine also has suggested benefit, indicating that the benefit is possibly a class effect.

The ACOG states that the use of nonhormonal therapies is a level C recommendation (results based on observational studies). In addition, ACOG notes that botanicals should not be considered in women with estrogen-dependent cancers. The North American Menopause Society states that alternative therapies have not been efficacious, except for moderate to large quantities of soy products (45–60 g/day soy protein). However, ACOG advocates behavior changes, such as increasing moderate exercise, avoiding hot flash triggers, and pacing respirations (deep, slow abdominal breathing). Evidence for phytoestrogens in menopausal women comes mostly from epidemiological studies, and long-term effects of these agents are not known. For these reasons, pharmacists should caution patients about using these agents on a chronic basis and patients should be advised to discuss these agents' use with their health care provider.

Atrophic Vaginitis/Genitourinary Symptoms

Introduction

As women transition into menopause, vulvovaginal atrophy and urinary tract conditions may manifest. In fact, up to 40% of postmenopausal women will suffer from atrophic vaginitis. Genital symptoms may include dryness,

Table 1-6. Oral, Transdermal, and Topical Hormone Therapies

Product	Typical Dosage Range
Conjugated estrogen	
Premarin (oral, vaginal cream)	0.3–0.625 mg/day (oral); 0.5–2 g/day (vaginal cream)
Prempro, Premphase (conjugated estrogen with medroxyprogesterone)	0.625/2.5 mg/day (Prempro); 0.625/5 mg/day (Prempro, Premphase)
Esterified estrogen	
Estratab	0.3–0.625 mg/day
Estratest, Estratest HS (esterified estrogen with methyltestosterone)	1.25/2.5 mg/day (Estratest); 0.625/1.25 mg/day (Estratest HS)
Estradiol	
Estrace (oral, vaginal cream)	0.5–1 mg/day (oral); 1 g 1–3 times/week (vaginal cream);
Climara, Estraderm, Vivelle, Alora, FemPatch (transdermal)	0.025–0.05 mg, changed weekly (Climara);
Vagifem (vaginal tablet)	0.025–0.05 mg,changed 2 times/week (Estraderm,
Estring (vaginal ring)	FemPatch,Vivelle, Alora); one tablet 2 times/week
Estrasorb (topical emulsion)	(Vagifem); one ring every 3 months (Estring); apply every day (Estrasorb)
Activella (estradiol with norethindrone)	1.0/0.5 mg/day
FemHRT (ethinyl estradiol with norethindrone)	5 mcg/1 mg/day
Ortho-Prefest (estradiol with norgestimate)	1.0/0.09 mg/day
Combipatch (estradiol with norethindrone)	0.05/0.14 or 0.05/0.25 mg 2 times/week
Climara Pro (estradiol with levonorgestrel)	0.045/0.015 mg once weekly
Estropipate	
Ogen, Ortho-Est (oral, vaginal cream)	0.625 mg/day (oral); 2–4 mg/day, cyclic (vaginal cream)
Synthetic conjugated estrogen	
Cenestin (oral)	0.625–1.25 mg/day

burning, dyspareunia, loss of vaginal secretions, and vulvar pruritus. Over time, lack of vaginal lubrication may lead to sexual dysfunction and subsequent emotional distress. Urinary symptoms may include urethral discomfort, frequency, dysuria, stress incontinence, and increased urinary tract infections. An increase in the severity of symptoms occurs in women who smoke cigarettes, have not experienced a vaginal birth, and who exhibit nonfluctuating levels of estrogen. Lesser symptoms occur in women who remain sexually active, have elevated androgen levels, and who have not undergone urogenital surgery.

Etiology

Because estrogen maintains vaginal mucosal integrity, a decrease in levels of circulating estrogen is the primary cause of vaginal atrophy. These decreases in estrogen may be because of the natural process of menopause, the use of antiestrogen drugs or treatments, such as chemotherapy and radiation.

Management

Hormone Therapy

As with vasomotor symptoms, estrogen therapy is the primary treatment for vaginal atrophy. Multiple randomized, controlled trials have shown significant improvements in urogenital symptoms, regardless of the administration route (oral, transdermal, and intravaginal). Table 1-6 lists oral, transdermal, and intravaginal products currently available. For women who have vaginal symptoms alone, a topical estrogen product (creams, pessaries, and hormone-releasing ring) are the most prudent option. For women who also may suffer from bone loss and/or hot flashes, systemic administration may be most effective; however, the overall benefits and risks of hormone therapy must be taken into account in each individual patient. The amount of estrogen and the duration of time required to produce benefit depends greatly on the degree of vaginal atrophy and varies widely among patients. Women who should not take hormone therapy have been discussed previously.

Moisturizers/Lubricants

Over-the-counter moisturizers and lubricants may be used in women with mild symptoms or in combination with hormone therapy in those with moderate to severe symptoms. Moisturizers help to maintain natural vaginal secretions and improve coital comfort; however, these products do not last long and must be reapplied frequently.

Other

Treatment with hormone therapy may help urinary symptoms as well, especially for women who suffer from stress incontinence (sphincter insufficiency). However, Kegel exercises and anticholinergic drugs also may prove useful. Agents, such as oxybutynin, tolterodine, and hyoscyamine, are useful for urge incontinence (detrusor instability). On the other hand, bethanechol, a cholinergic agonist, has been useful for atonic bladder (overflow).

Table 1-7. Nonhormonal Therapies for Vasomotor Symptoms

Agent	Comment
Exercise	Single observational study has shown benefit
Soy/isoflavones	Multiple randomized, controlled trials with conflicting results. No formal meta-analysis. 45–60 g/day recommended
Clonidine	Multiple small randomized, controlled trials have shown benefit (0.1–0.4 mg/day)
Venlafaxine	Single randomized, controlled trial (in women with breast cancer, most of whom were taking antiestrogen therapy) has shown benefit (12.5 mg 2 times/day)
Fluoxetine	Single randomized, controlled trial (in women with breast cancer, most of whom were on antiestrogen therapy) has shown benefit (20 mg/day)
Gabapentin	Single randomized, controlled trial has shown benefit (900 mg/day)
Megestrol	Single randomized, controlled trial (in women with breast cancer, most of whom were taking antiestrogen therapy) has shown benefit (40 mg/day)
Black cohosh	German E commission recommendation in 1989 (40–80 mg/day); recent randomized, controlled trial showed no benefit. Safety of agent controversial
Other	
Bellergal, methyldopa, evening primrose oil, ginseng, wild yam extract, dong quai, and flaxseed	All have been advocated; however, there is no evidence of efficacy

Health care professionals need to educate older women about the potential side effects of anticholinergic drugs, such as dry mouth, blurred vision, constipation, and confusion, because this may limit their use. Women with frequent urinary tract infections (more than three per year) may benefit from prophylactic therapy with trimethoprim-sulfamethoxazole or nitrofurantoin.

Vaginal atrophy and urinary symptoms also may lead to sexual dysfunction in some women. Although female sexual dysfunction often is complicated by psychological aspects as well, many of the previously discussed treatments, such as hormone therapy and the use of moisturizers/lubricants, may be useful. This is particularly true if there is a disorder of arousal or if there is painful intercourse because of vaginal dryness. In the case of decreased libido (disorder of desire), the use of testosterone has significant benefits. A combination estrogen-testosterone product can be recommended in this situation. Because there currently is no commercially available topical testosterone product for women, many health care providers are recommending compounded topical preparations (1–2% ointment or gel, one-fourth teaspoonful applied to the genital area no more than once per day). Pharmacists should understand this disorder, recognize currently available treatment options, and be able to counsel patients effectively on topical preparations' use and potential side effects. There is still much research that needs to be completed regarding appropriate treatments for female sexual dysfunction.

Mood Disorders

Introduction

Studies of depressive symptoms in menopausal women indicate that menopause is not necessarily associated with increased rates of depression; however, symptoms, such as mood changes, depression, poor concentration, and impaired memory have been noted in these women. Women with a previous history of depression or other affective disorder may be at increased risk for alterations in mood.

Etiology

Neurobiological effects of estrogen include decreased monoamine oxidase activity, enhancement of serotonin neurotransmission and cholinergic transmission, antidopaminergic effects in certain brain areas, modulation of gamma aminobutyrate receptors and progesterone receptors, and modification of sleep and circadian rhythms. It is thought that the decrease in circulating estrogen levels during menopause causes dysregulation of several neurotransmitter and neuromodulatory systems such that mood changes may occur. However, psychosocial factors also may contribute to mood changes during this phase of life, such as stress from dealing with teenage children, onset of major illness, caring for an aging parent, divorce or widowhood, career change, or retirement. In addition, the signal of the end of fertility may be perceived as a significant loss and the fear of aging itself may cause great anxiety. Women who suffer from sleep deprivation as a result of hot flashes and night sweats also may be moody and irritable. As can be determined, the cause of these

psychological effects is complex and encompasses a wide variety of issues.

Management

Hormone Therapy

As with other menopausal symptoms, hormone therapy can be used for psychological symptoms. Recent studies have suggested that estrogen use is associated with a significant improvement in mood for depressed perimenopausal and menopausal women. In addition, some epidemiological studies indicate that estrogen use is associated with improved verbal and visual short-term memory performance and overall increased quality of life. However, it must be remembered that this is likely the result of an overall improvement in menopausal symptoms and that these results should not be extrapolated to asymptomatic menopausal women. Table 1-6 lists currently available hormone therapies in various dosage forms; however, it should be noted that the studies examining cognitive function and mood were completed with systemic formulations only. The psychological effects of progesterone and androgens have been less extensively studied than those of estrogen and further research is needed with these agents. A list of women who should not take hormone therapy has been discussed previously and, again, the benefits and risks of treatment should be seriously weighed according to each individual situation. It also should be noted that at this time, there are no published long-term, prospective, randomized, controlled studies that show beneficial effects of estrogen on the incidence or progression of Alzheimer's disease. Therefore, the use of hormone therapy to protect against this disease should not be recommended.

Other

Health care providers can help alleviate fear by educating women on what physiological and psychological changes to expect during menopause. Non-pharmacological therapies, such as relaxation and stress-reduction techniques; increases in exercise; and decreases in smoking and alcohol consumption, may help some women. It typically is noted that if symptoms persist after hormone therapy and/or non-pharmacological interventions or the symptoms are clinically severe, antidepressant drugs can then be considered. In general, selective serotonin reuptake inhibitors are the antidepressants of choice for menopausal women because they also have beneficial effects on reducing hot flashes and night sweats.

Hormone Therapy: Risks and Benefits

Introduction

Throughout the early and mid 1990s, observational and epidemiological data strongly suggested that hormone replacement therapy in postmenopausal women would play a key role in reducing the risk for many long-term consequences of estrogen deficiency, such as osteoporosis, heart disease, and cognitive decline. This made sense for several reasons. First, the risk of heart disease was much less in premenopausal women compared to men of the same age, but increased to a similar rate after menopause. Observational studies reported that taking estrogen reduced postmenopausal cardiovascular risk by 35–50%. Human and animal data supported mechanistically that estrogen raises high-density lipoprotein cholesterol, lowers low-density lipoprotein cholesterol, reduces fibrinogen, raises levels of some natural clot inhibitors, and improves arterial wall elasticity. Second, numerous prospective studies demonstrated that the increased bone turnover leading to osteoporosis resulting from estrogen loss could be stabilized by administration of estrogen in postmenopausal women. Third, emerging case-controlled, cross-sectional, and prospective data from elderly women suggested that those who had taken estrogen after menopause had less Alzheimer's disease or other cognitive decline, fueling an estrogen deficiency hypothesis as a factor for dementia.

However, speculative debates raged regarding the differences and similarities among the various hormone products or combinations of agents in their ability to produce the desired preventive outcomes. Beginning in the late 1990s, data from several large prospective trials began to emerge that reinforced the concept that postmenopausal estrogen therapy increases bone mineral density. However, there also have been concerns about an increased risk of atypical endometrial hyperplasia (a precursor to endometrial cancer) with unopposed estrogen use in women with an intact uterus (the number needed to harm = 4; Postmenopausal Estrogen/Progestin Interventions trial) and possible increase in breast cancer risk with prolonged hormone therapy. In addition, these trials began to refute some earlier assumptions, particularly regarding impact on heart disease.

Trials

In 1998, data were published from the prospective, double-blind, placebo-controlled Heart and Estrogen/Progestin Replacement Study (HERS) of 2763 postmenopausal women with coronary heart disease, average age 67 years. Investigators reported that 4.1 years average follow-up of hormone therapy with combined continuous CEE 0.625 mg plus MPA showed no advantage over a placebo in preventing coronary events in women with preexisting heart disease. Women taking hormones had 50% more coronary events than women receiving placebo during the first year of the 4-year trial, although this was offset by a 40% decrease in the past 2 years of the study. The increased risk in the initial year was primarily because of thromboembolic complications; however, the absolute risk was relatively small and the risk was highest in the first year of use (number needed to harm = 154; HERS). In addition, women taking hormones had an

Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/Progestin Replacement Study (HERS) Research Group. JAMA 1998;280:605–13.

increased risk of gallbladder disease, with 48% requiring surgery. The risk of gallbladder disease in women taking estrogen therapy increased by a factor of 2–3 versus women not on hormones (number needed to harm = 67; HERS). Ninety-three percent of the original HERS participants (n=2321) continued treatment for an additional 2.7 years (mean total, 6.8 years) in consultation with their physicians. In 2002, HERS II reported no benefit of long-term use of hormone therapy for any other major disease outcome, including overall risk of death.

The first randomized, prevention trial to include hormone therapy began in 1993 and was scheduled for completion in 2005. The Women's Health Initiative (WHI), sponsored by the National Heart, Lung, and Blood Institute, began studying ways to prevent heart disease, breast and colorectal cancer, and osteoporosis. It consisted of a set of three interrelated clinical trials and an observational study in more than 161,000 apparently healthy postmenopausal women 50–79 years of age (mean age, 63.2 years). The WHI had an arm of CEE-MPA for women with a uterus (n=16,608) and an estrogen-only arm (n=10,739) for women who had undergone a hysterectomy. In April 2000, participants were notified of a small, early increase in heart attacks, strokes, and blood clots in the lungs of women receiving CEE-MPA. In 2002, the CEE-MPA component was prematurely stopped after an average of 5.2 years follow-up when the data, safety, and monitoring board recommended stopping the trial because women receiving the CEE-MPA had an increased risk of invasive breast cancer (hazard ratio = 1.26; 95% confidence interval = 1–1.59). An overall measure suggested that the treatment was causing more harm than good (global index hazard ratio = 1.15; 95% confidence interval = 1.03–1.63). Risk increased for coronary heart disease (hazard ratio = 1.29; 95% confidence interval = 1.02–1.63), stroke (hazard ratio = 1.41; 95% confidence interval = 1.07–1.85), and pulmonary embolism (hazard ratio = 2.13; 95% confidence interval = 1.39–3.25).

The risk of colon cancer was reduced by 37% in the hormone therapy group (hazard ratio = 0.63; 95% confidence interval = 0.43–0.92). On average, annually there were 10 cases of colorectal cancer per 10,000 women receiving hormone therapy compared to 16 cases of colorectal cancer per 10,000 women receiving placebo. The benefit appeared after 3 years of use and became more significant over time. Risk also decreased for hip fracture (hazard ratio = 0.66; 95% confidence interval = 0.45–0.98). On average, annually there were 10 cases of hip fracture per 10,000 women receiving hormone therapy compared to 15 cases per 10,000 women receiving placebo. The number of overall deaths was statistically and clinically similar.

As previously suspected based on observational data, the risk for breast cancer while using continuous combined estrogen-progestin appears to be related to duration of use. The WHI investigators calculated that on average, per year, there were 38 cases of breast cancer per 10,000 women receiving hormone therapy compared to 30 breast cancer cases per 10,000 women receiving placebo. Thus, there were, on average, eight additional cases of breast cancer per 10,000 women per year in the hormone therapy group of the WHI study population. The increase in breast cancer was apparent after 4 years of hormone therapy use and the risk appears to be cumulative, increasing over time. However, although the increased risk for the group on hormone therapy was 26%, an individual woman's increased risk for breast cancer with hormone therapy use was less than 0.1% per year. The risk of death in women who developed breast cancer could not be compared because of the relatively short follow-up time.

Subsequent analyses from the CEE-MPA arm of the WHI continue to be published. Although WHI was not designed to evaluate hormone use in women with menopausal symptoms (an exclusion criteria), an evaluation of quality of life in WHI participants found that CEE-MPA did not have a meaningful impact on the quality of life in this asymptomatic population. The CEE-MPA combination also has not improved cognitive function compared to placebo and may have increased the risk of probable dementia in participants in the WHI who were older than 65 years of age. Ischemic stroke and invasive ovarian cancer also were found more frequently in the CEE-MPA participants. The CEE-MPA combination increased bone density and reduced the risk of fracture in healthy postmenopausal women regardless of age, body mass index, smoking status, history of falls, personal and family history of fracture, total calcium intake, past use of hormone therapy, bone mineral density, or summary fracture risk score. However, this benefit did not produce a net advantage when considering the effects of hormone therapy

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on other important disease outcomes in a global model, even in women at a high risk of fracture.

On February 2, 2004, with an average of almost 7 years of follow-up completed, the estrogen-only arm (CEE) of the WHI was discontinued by the National Institutes of Health. Data found that CEE alone does not appear to affect (either increase or decrease) heart disease. The risk of breast cancer was not increased during the time period of the study and the risk of hip fracture actually decreased. However, CEE alone appeared to increase the risk of stroke, similar to what was found in the WHI study of CEE-MPA. The National Institutes of Health determined that enough data have been obtained to assess the overall risks and benefits of the use of estrogen in this trial and the apparent increased risk of stroke in previously healthy women participating in a research study was not acceptable to allow the study to continue to its original planned completion in 2005. The ancillary WHI studies evaluating low-fat diet, calcium, and vitamin D are continuing.

Although the results from HERS or WHI do not necessarily apply to lower CEE and MPA doses, other oral estrogens and progestins, or transdermal estrogens and progestins, it is difficult not to extrapolate the findings to all forms of hormone replacement until there are sufficient data to suggest otherwise. Many experts are speculating on the impact of the type of estrogen or progestin, dose, regimen, or delivery system. There is an emerging theory that estrogen protects against the earliest stages of atherosclerosis but may precipitate clinical events in women with existing (albeit subclinical) atherosclerosis. Another hypothesis suggests that transdermal estradiol, which more closely mimics human physiology, may be more appropriate than oral estrogens. Similarly, as progestins are being scrutinized, various regimens using natural micronized progesterone or longer intervals between cyclic progestin therapy (i.e., every 3 months) are being discussed.

The Women's International Study of long Duration Oestrogen after Menopause was a large, long-term, prospective, prevention trial to be conducted over a 10-year treatment period in 14 countries and coordinated by the London-based Medical Research Council. The Women's International Study of long Duration Oestrogen after Menopause was to evaluate the role of hormone replacement therapies similar to those studied in WHI on a variety of women's health concerns, including cardiovascular disease and osteoporosis. Although no safety concerns were cited, the Women's International Study of long Duration Oestrogen after Menopause was discontinued after release of the WHI and because the results would be unlikely to influence clinical practice.

The Estrogen Therapy for Prevention of Reinfarction in Postmenopausal Women Trial found that unopposed oral estradiol did not protect postmenopausal women against reinfarction and cardiac death. Postmenopausal women 50–69 years of age who survived a first myocardial infarction were enrolled in Estrogen Therapy for Prevention of Reinfarction in Postmenopausal Women Trial and randomized to unopposed oral estradiol valerate 2 mg/day (n=513) or placebo (n=504) for 2 years. Estradiol, started within weeks of an initial myocardial infarction, did not show either benefit or harm for coronary heart disease, but the interpretation of the result is limited by the lack of statistical power and poor compliance (43% in the estradiol group and 64% in the placebo group).

The Papworth HRT and Atherosclerosis Study, a British study of postmenopausal women with angiographically proven ischemic heart disease who received either transdermal estrogen (with or without a progestin) or a placebo, was stopped early because of no apparent benefit. However, the estradiol group had a higher, but not statistically significant, event rate than the control group, particularly during the first 2 years of follow-up.

Between 1996 and 2001, more than 1 million women 50–64 years of age in the United Kingdom were recruited to provide information about their use of hormone therapy and were followed for cancer incidence and death. The recently published results of the Million Women Study found that current users of hormone at recruitment were more likely than never users to develop breast cancer (adjusted relative risk = 1.66) and die from it (adjusted relative risk = 1.22). The relative risk of breast cancer in current users increased with longer duration of use. Past users of hormone did not have an increased risk of incident or fatal disease (relative risk = 1.0 and 1.05, respectively). This risk was higher in women who used estrogen plus progestin (relative risk = 2.00) than those who used estrogen alone (relative risk = 1.30). Investigators estimated that throughout the past decade, hormone therapy resulted in an extra 20,000 incidents of breast cancers and the estrogen-progestin combinations accounted for 15,000 of these additional cancers. Results varied little between specific estrogens and progestins or their doses, or between continuous and sequential regimens. There was no difference in risk found between oral estrogen users and users of transdermal estrogen.

Cauley JA, Robbins J, Chen Z, et al. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. JAMA 2003;290:1729–38.

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Beral V; Million Women Study Collaborators. Breast cancer and hormone replacement therapy in the Million Women Study. Lancet 2003;362:419–27.

Abbreviations

Impact on Place in Therapy

In all women, the consideration for use of hormone therapy must be individualized for the particular patient, based on menopausal symptoms and risk factors. Women should be encouraged to maintain a regular schedule of mammograms and breast self-examinations. Based on data from the WHI, the FDA published labeling changes required for all postmenopausal hormone therapies containing estrogen alone or estrogen plus progestin. The following are some key points from FDA labeling revisions:

- Labeling changes apply to all estrogen alone and estrogen plus progestin products marketed, and the FDA will issue labeling guidance instructions for all manufacturers of these products.
- The boxed warning highlights the increased risk for heart disease, myocardial infarction, stroke, and breast cancer.
- Indications for vulvar and vaginal atrophy are revised to state that they are for treating moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause. Furthermore, when used solely for this indication, topical vaginal products should be considered.
- The indication for preventing postmenopausal osteoporosis is revised to state that when estrogen or estrogen plus progestin therapy is used solely for this indication, approved nonestrogen treatments should be carefully considered, and these hormonal products should only be considered for women with significant risk of osteoporosis that outweighs the risks of the drug.
- Labeling advises clinicians to prescribe the lowest dose for the shortest duration of time.
- Because there are few alternatives for the relief of severe vasomotor symptoms, the FDA notes that estrogen and estrogen plus progestin have an important role in women's health, and in many cases, women will want to rely on these products to deal with the effects of menopause.
- Labeling revisions also emphasize the importance of making individualized decisions that appropriately balance the benefits and the potential risks of these products.

Cardiovascular Disease: Hormone (estrogen plus progestin or estrogen alone) therapy is NOT indicated for treating or preventing heart disease. Hormone therapy being taken solely for this reason should be discontinued, tapered if possible. Women at risk for heart disease and their health care providers should enhance traditional measures to prevent cardiovascular disease, including smoking cessation, regular exercise, treatment of hypertension and dyslipidemia, and maintenance of appropriate weight.

Vasomotor Symptoms: Estrogen remains the most effective therapy for vasomotor symptoms. No data from new studies or others suggest that women should discontinue hormone therapy or avoid its use for managing hot flashes and night sweats. However, if hormone therapy is used for moderate to severe vasomotor symptoms, the dose should be as low as possible to control symptoms and duration of use should be less than 5 years. Interest in use of progestins other than MPA should increase (i.e., micronized progesterone, norethindrone acetate, and norgestimate). Use of nonoral routes of estrogen as well as lower doses of hormones also should increase. "Nontraditional" regimens using continuous estrogen combined with "seasonal" cyclic progestin (e.g., 2 weeks of progestin every 2–3 months) or the levonorgestrel IUD may be an option. Some perimenopausal women take low-dose oral contraceptives to control vasomotor symptoms. The WHI data reemphasize the fact that COC use increases the risk of thromboembolism and should not be used in perimenopausal women who smoke or who are, for other reasons, at elevated risk for arterial vascular events.

Atrophic vaginitis: Recommend the use of lubricants for intercourse and consider vaginal estrogen products as previously discussed in more detail.

Osteoporosis: Hormone therapy was effective in increasing bone mineral density and reducing hip fractures in the WHI data. This was notable given that the population being studied did not have established or preexisting osteoporosis and a benefit was seen within the 5-year study period. Because the trial was stopped prematurely, fracture prevention may have been more evident if it had continued for the planned 8 years. Initiation of hormone therapy in a woman with a uterus soon after menopause for preventing bone loss is still appropriate and data suggest that low-dose estrogen is effective in preventing bone loss. However, risk may outweigh the benefit after a few years of use and traditional measures to prevent and treat osteoporosis should be encouraged. These include adequate calcium and vitamin D intake, smoking cessation, regular weight-bearing exercise, bone density testing (if appropriate in people at high-risk), and increased focus on bisphosphonates and raloxifene.

Conclusion

Women's health encompasses a variety of issues, ranging from PMS and contraception in premenopausal women to vasomotor symptoms and the use of hormone therapy in postmenopausal women. It is important for pharmacists to be able to design the best contraceptive management plan for a patient; demonstrate an understanding of how to treat menstrual-related disorders, such as PMS, DUB, and dysmenorrhea; develop an appropriate management plan for a woman complaining of menopausal symptoms and evaluate outcome data on the use of hormones to make informed recommendations and counsel women effectively. As providers of drug information, pharmacists should take responsibility for keeping up with the literature and understanding the benefits and risks associated with the various therapies discussed within this chapter.

Annotated Bibliography

1. Dickey RP. Managing Contraceptive Pill Patients, 11th ed. Durant, OK: Essential Medical Information Systems Inc., 2002.

   This popular book is a practical source of information for health care professionals who provide drug information related to hormonal contraception. Individual chapters are devoted to various products, including oral contraceptives,

injectable and implantable products, and emergency contraception. This book remains the only single source for information about differences among oral contraceptives regarding estrogenic, androgenic, progestational, and endometrial potencies and management of side effects in relation to these differences. In addition, there are multiple tables with comparative oral contraceptive information, such as composition, effects on lipid profile and choice of initial agent. Potential laboratory changes and drug interactions are also included in table format. A limitation is the lack of information on nonhormonal contraception.

2. Contraception Online Web site. Available at *www.contraceptiononline.org*. Accessed September 15, 2003.

   This Web site provides useful information for clinicians, researchers, and educators about nonhormonal and hormonal contraception. The goal is to explore important issues related to reproductive health in a scientific and objective manner to provide practical educational tools and materials for both health care professionals and patients. More specifically, the Web site contains up-to-date information on reproductive health, family planning, and contraception and is guided by a National Advisory Panel that includes experts in these fields. The Web site also includes slide sets and continuing education for health care professionals as well as the online version of the Contraception Report.

3. American College of Obstetricians and Gynecologists Web site. Available at *www.acog.com*. Accessed September 20, 2003.

   The American College of Obstetricians and Gynecologists (ACOG) is the world's leading group of professionals providing health care for women, and this Web site provides information related to a variety of women's health issues, including contraception, postmenopausal disorders, premenstrual syndrome (PMS), premenstrual dysphoric disorder, and infertility. The goal of the organization is to serve as a strong advocate for quality health care for women, maintain the highest standards of clinical practice and continuing education for its members, promote patient education, stimulate patient understanding of and involvement in medical care, and increase awareness among its members and the public of the changing issues facing women's health care. The Web site reflects these four key goals. Health care professionals can order a variety of educational materials and gain access to up-to-date news releases and ACOG practice bulletins, and statements.

4. Munro MG. Medical management of abnormal uterine bleeding. Obstet Gynecol Clin North Am 2000;27(2):287–304.

   This article, written by a leading expert in the area, discusses the medical management of abnormal uterine bleeding, including a variety of therapeutic options. By providing an understanding of the biology of menstruation and the pathogenesis of mechanisms involved in uterine bleeding, the author provides the rationale for and appropriate application of these treatments. More specifically, there is a discussion regarding the distinguishing features of abnormal bleeding associated with ovulation compared to that which is anovulatory in nature. The article also clearly defines mild, moderate, and severe disorders. The author makes note that even though there is clearly a role for surgery with some of these patients, medical therapy has enormous potential for most women with dysfunctional uterine bleeding.

5. Clinical Management Guidelines for Premenstrual Syndrome. ACOG Practice Bulletin. No. 15. Washington, D.C.: The American College of Obstetricians and Gynecologists, April 2000.

   This practice bulletin was developed by the ACOG Committee on Practice Bulletins and is designed to aid practitioners in making appropriate decisions for patients with PMS. It contains general information on epidemiology, risk factors, etiology, and clinical considerations/recommendations. The article contains specific information on both non-pharmacological and pharmacological treatment options, from aerobic exercise and dietary supplementation to the use of selective serotonin reuptake inhibitors and combined oral contraceptives. In addition, the bulletin does an excellent job of referencing the evidence behind the various recommendations and summarizes the stepwise approach to care.

6. The North American Menopause Society Web site. Available at *www.menopause.org*. Accessed January 28, 2004.

   This is the Web site of the North American Menopause Society, the leading scientific nonprofit organization devoted to promoting women's health during midlife and beyond through an understanding of menopause. This is an overall excellent source for up-to-date information on menopause and the potential treatment options for those who suffer from disorders related to menopause. This site contains specific information on perimenopause, early menopause, menopause symptoms, long-term health effects of estrogen loss, and a wide variety of therapies to enhance health. Health care professionals can benefit from the scientific news and press releases, whereas consumers can benefit from the educational materials provided.

Abbreviations

Please start new PSAP-V answer sheet before continuing.

SELF-ASSESSMENT QUESTIONS

1. You are helping a patient determine an appropriate method of contraception for her personal situation. You suggest the medroxyprogesterone acetate (MPA) injection. Based on this recommendation, which one of the following conditions most likely represents your patient's situation?
   A. She is human immunodeficiency virus positive.
   B. She wants to get pregnant in about 6–8 months.
   C. She is a smoker older than 35 years of age.
   D. She is overweight.

Question 2 pertains to the following table.

Choice	Endometrial Activity	Estrogenic Activity: mcg ethinyl estradiol equivalents/day	Progestational Activity: mg norethindrone equivalents/day	Androgenic Activity: mg methyltestosterone/ 28 days
1	9.6	25	0.8	0.46
2	26.5	17	0.5	0.31
3	37.4	19	1.4	0.21
4	29.7	13	1.2	0.53
5	14.3	35	0.3	0.18

2. C.S. is a 29-year-old woman who returns to your clinic today requesting an oral contraceptive. Her past medical history and physical examination are unremarkable. Her only drug is retin-A for acne. Which one of the following is the best choice for C.S.?
   A. 1.
   B. 5.
   C. 4.
   D. 2.

3. A 45-year-old woman complains of irregular menstrual cycles and occasional hot flashes. She is otherwise healthy and does not smoke cigarettes or use alcohol. You diagnose her as perimenopausal. Which one of the following is the best choice to treat her symptoms?
   A. Estradiol 1 mg plus norethindrone 0.5 mg, one tablet orally every day.
   B. Conjugated estrogens 0.625 mg, one tablet orally every day.
   C. Estradiol 0.05 mg/day plus norethindrone 0.14 mg/day, one patch 2 times/week.
   D. Ethinyl estradiol 35 mcg plus norethindrone 1 mg, one tablet orally every day.

4. Which one of the following is a noncontraceptive benefit of oral contraceptives?
   A. Prevention of cervical cancer.
   B. Decreased serum triglyceride concentrations.
   C. Protection against many sexually transmitted diseases.
   D. Decreased risk of endometrial and ovarian cancers.

5. A 19-year-old college student calls you at 8 AM on Friday in a panic. She and her partner were at a party the previous night, had too much to drink, and had spontaneous intercourse without protection. Because the act occurred less than 72 hours ago, you decide to recommend emergency contraception. Which one of the following is an advantage of high-dose progestin-only pills over combined contraceptive regimens for emergency contraception?
   A. They will be effective if given within 5 days of unprotected intercourse.
   B. They are less expensive.
   C. They cause less nausea and vomiting.
   D. The progestin-only regimen requires only one dose instead of two.

6. S.S. is a 28-year-old woman who has been taking a 35-mcg combined oral contraceptive (COC) as her hormonal contraceptive for about 1 year. Her mother recently was diagnosed with breast cancer, but no other significant family history exists. S.S.'s medical history is nonsignificant and she currently takes no other routine drugs. S.S. comes into the clinic today questioning the use of her COC and wondering if it will increase her risk of breast cancer. S.S. wants to know your thoughts on the subject. Which one of the following is the best response?

   A. Combined oral contraceptives are contraindicated in women with a family history of breast cancer. Discontinue the drug and switch to a progesterone-only product.
   B. There has never been any evidence of a relationship between the use of COCs and the risk of breast cancer in women with a family history of the disease. She can continue the COC because she is otherwise an appropriate candidate.
   C. Based on recent data, there is little to no additional risk of breast cancer in women who use COCs and had a family history of the disease. She can continue the COC because she is otherwise an appropriate candidate.
   D. A significant increased risk of metastatic breast cancer was found in women who used COCs and had a family history of the disease. Therefore, the risks outweigh the benefits and the COC should be discontinued and a progesterone-only product should be initiated.

7. B.B. is a woman who calls the clinic where you are working and states that she has been out of town for the past 2 days and forgot to take her oral contraceptives with her. Consequently, she has missed 2 days of tablets (in week 2) and wants to know what she should do. She has not had unprotected intercourse during this time. Which one of the following is the best response that you can give B.B. at this time?

   A. Continue taking her tablets on a regular schedule. Use additional contraception for the remainder of the cycle.
   B. Take two tablets daily for the next 2 days and then resume taking her tablets on a regular schedule. Use additional contraception for the remainder of the cycle.
   C. Begin a new pack and use additional contraception for the next 7 days.
   D. Stop taking the tablets. Prescribe the transdermal patch for her.

8. T.F. is a 36-year-old teacher who is going on a trip out of the country with her husband. She has been taking a 20-mcg COC for the past 8 years with no problems. She is taking doxycycline for malaria prophylaxis and ciprofloxacin to prevent and treat traveler's diarrhea. Which one of the following recommendations is best for T.F.?

   A. Switch to a high-dose estrogen oral contraceptive pill to overcome the loss of estrogen effectiveness caused by the concurrent antibiotics.
   B. Change to the vaginal ring.
   C. Make no change to her current regimen because there is no evidence that antibiotics will interfere with T.F.'s contraceptive method.
   D. Add a barrier method to her current regimen while she is taking the antibiotics and for 7 days after stopping them.

9. J.H. is a 22-year-old college student who complains of irritability, depression, bloating, breast tenderness, and headache for the few days before menses each month. She states that these symptoms usually keep her from going to classes and work for at least 2 days each month. J.H. says ibuprofen helps with the headaches, but she has found no relief from the other symptoms and wants help. Which one of the following treatment recommendations for J.H. is best at this point?

   A. Encourage aerobic exercise and vitamin supplementation.
   B. Recommend the use of a low-dose oral contraceptive.
   C. Recommend the use of a selective serotonin reuptake inhibitor, such as fluoxetine.
   D. Recommend spironolactone.

Questions 10–12 pertain to the following case.

Y.J., a 15-year-old girl, experienced her first menstrual period at 13 years of age. Since then, she has been irregular and most recently has been having a cycle with heavy flow (soaking 8–10 pads/day) every 2–3 weeks. She is brought to the medical center after fainting in class. On questioning, she admits that she recently fainted twice during soccer practice and is having a heavy period this week. Laboratory results reveal that her hemoglobin is low (6.4 g/dl) and a pregnancy test is negative.

10. Which one of the following is the best initial therapy for Y.J.'s abnormal uterine bleeding?

    A. Oral progestin for 12–14 days.
    B. Intravenous estrogen for 12–24 hours.
    C. Oral contraceptive (typical dosing).
    D. Oral contraceptive (accelerated dosing).

11. Which one of the following adjunctive therapies should be offered to Y.J. at this time?

    A. Ibuprofen.
    B. Fluoxetine.
    C. Meclizine.
    D. Magnesium.

12. Y.J. was found to have dysfunctional uterine bleeding (DUB) without any underlying secondary cause. Once her bleeding is under control, which one of the following therapies should be started?

A. Combined oral contraceptive, one tablet 4 times/day for 2 days, then tapered over the following week.
B. Conjugated estrogen 0.3 mg/day.
C. Estradiol patch 0.025 mg changed 2 times/week.
D. Estradiol vaginal ring 2 mg inserted every 3 months.

13. R.R. is a 28-year-old woman who complains of lower abdominal pain with the onset of menses. She states that the pain is causing lost work days and decreased productivity, and she has tried nonsteroidal anti-inflammatory drugs (NSAIDs) (ibuprofen 200–400 mg 3 times/day during the most painful days) in the past with limited success. Which one of the following is R.R. suffering from and which one of the following treatment recommendations would you make for her at this time?

A. Dysmenorrhea; recommend a monophasic oral contraceptive because ibuprofen has shown little success.
B. Premenstrual syndrome (PMS); recommend the addition of a selective serotonin reuptake inhibitor, such as fluoxetine, in addition to exercise and a healthy diet.
C. Dysmenorrhea; increase the dose of the ibuprofen (up to 400–600 mg every 4–6 hours).
D. Premenstrual syndrome; recommend a more potent NSAID, such as indomethacin, to better control pain.

14. Which one of the following statements about PMS/premenstrual dysphoric disorder is correct?

A. Premenstrual dysphoric disorder is a variant of PMS that presents with less severe psychological symptoms.
B. There is little to no evidence for the role of non-pharmacological treatment strategies in PMS.
C. Diuretics, such as furosemide, are recommended as first-line treatment for patients who suffer from bloating and edema.
D. According to the American College of Obstetricians and Gynecologists (ACOG), patients must suffer from at least one emotional and one physical sign/symptom to be diagnosed with PMS.

Questions 15–17 pertain to the following case.

E.F. is a 47-year-old Caucasian woman with a 6-month history of chest palpitations and sudden feelings of warmth over her chest, accompanied by a patchy flushing of her skin during the past month. She also complains of not sleeping well lately and being quite moody or anxious at times. She has been having irregular periods for the past 2 years, but recently the bleeding may last 10–15 days with heavy blood loss and clots. She is 5'5" tall, weighs 150 pounds, and has no other medical conditions and no significant family history for cancer or heart disease. She currently is experiencing a heavy menstrual bleed that is in its eighth day; she has a prescription for 10 days of MPA 10 mg and a 3-month supply of an oral contraceptive (triphasic norgestimate-35 mcg ethinyl estradiol). She knows that the doctor told her to start taking the progestin today and start taking the oral contraceptive a week after her last dose of MPA. However, she is still confused about the bleeding.

15. Which one of the following should you tell E.F. to expect regarding vaginal bleeding?

A. The bleeding should stop or diminish while she takes the MPA and she should bleed for only a few days after the MPA is finished.
B. She should continue to bleed during the MPA and stop only after she finishes the first month of oral contraceptive.
C. The bleeding should get worse while she is taking the MPA but stop when she finishes the MPA.
D. The bleeding should stop within 1–2 days of starting MPA and not start again until she finishes the first pack of oral contraceptive.

16. Which one of the following is best for E.F. after the 3 months of an oral contraceptive?

A. Continue the current oral contraceptive for another 3–6 months and reassess.
B. Transdermal estrogen patch.
C. Conjugated equine estrogen.
D. Discontinue the oral contraceptive and begin black cohosh.

17. E.F. also wants to know about the overall use of hormones in light of the news from the Women's Health Initiative (WHI) data that she heard. Which one of the following is the best response to E.F.'s question?

A. Estrogen therapy has no use in most postmenopausal women.
B. Transdermal and other nonoral estrogens are likely to be safer, even in women with a history of breast cancer.
C. The benefits and risks of postmenopausal use must be individualized, but in general, estrogen therapy and estrogen-progestin therapy remain the most effective short-term treatment option for menopausal symptoms.
D. Compounded natural estrogens and progesterone products are safe and effective for use in postmenopausal women compared to the drugs studied in the WHI.

18. Which one of the following best summarizes the effects of postmenopausal estrogen replacement on lipid profiles?

A. Decreases both low-density lipoprotein and high-density lipoprotein cholesterol.
B. Increases low-density lipoprotein cholesterol and decreases high-density lipoprotein cholesterol.
C. Increases both triglyceride concentrations and high-density lipoprotein cholesterol.

D. Decreases both triglyceride concentrations and low-density lipoprotein cholesterol.

19. Which one of the following conditions typically improves within the first 1–2 years after the onset of menopause, without the use of additional therapy?

A. Hot flashes.
B. Osteoporosis.
C. Angina.
D. Atrophic vaginitis.

20. A 72-year-old woman comes to you with complaints of vaginal dryness and decreased lubrication. She says it is affecting her "love life". Her medical history is significant for hypertension, type 2 diabetes mellitus, and coronary artery disease. Her drug regimen includes metoprolol 100 mg orally 2 times/day, hydrochlorothiazide 25 mg orally every day, atorvastatin 10 mg orally 2 times/day, metformin 1000 mg orally 2 times/day, and aspirin 81 mg orally every day. Surgical history indicates that she has had a hysterectomy. Which one of the following potential treatments is best to recommend in this patient?

A. Conjugated equine estrogen (CEE) 0.625 mg.
B. Conjugated equine estrogen-MPA 0.625/2.5 mg.
C. Evening primrose oil.
D. Vaginal estradiol 25-mcg tablet.

21. M.H. is a 48-year-old woman who has been taking a low-dose COC for about 1 year during perimenopause. She is now considered fully menopausal and is worried about switching to hormone replacement therapy. She is questioning what she can use that has evidence of alleviating hot flashes and mood swings. Her medical history is significant for osteoarthritis and asthma. She has not had a hysterectomy. Which one of the following is the best treatment recommendation?

A. Estrogen therapy (CEE) should be encouraged short term (1–2 years).
B. A selective serotonin reuptake inhibitor, such as fluoxetine, in addition to stress reduction and relaxation techniques.
C. Continue the COC for 1–2 years until the menopausal symptoms have most likely resolved.
D. Clonidine in addition to stress reduction and relaxation techniques.

22. J.L. is a healthy 43-year-old woman who recently had a hysterectomy because of uncontrolled DUB and has been using an estradiol transdermal patch for 3 months to control severe menopausal symptoms. She does not have a personal or family history of breast cancer or clotting disorders, but there is a history of heart disease in the family. When asked about continuing the estrogen patch in J.L., which one of the following recommendations is best at this time?

A. Continue treatment, but recommend short term.
B. Continue treatment but switch to an oral estrogen.
C. Continue treatment but add a progestin 12–14 days/month.
D. Discontinue treatment immediately.

23. S.T. is a 56-year-old woman who has been taking hormone therapy (estrogen-progestin combination) for 7 years. She was started on this drug after experiencing hot flashes at the beginning of menopause. She has no cardiovascular disease or history of breast cancer in her family but has risk factors for osteoporosis. She has no current complaints. S.T. is now in the clinic for a routine annual examination and her physician asks for your opinion on whether she should continue the drug. Which one of the following is the best response to S.T.'s question?

A. Taper the drug because her hot flashes are probably not an issue 7 years after the start of menopause, and the results of recent trials have shown no cardiovascular benefit of hormone therapy.
B. Continue the drug because she has risk factors for osteoporosis, no complaints at this time, and no history of breast cancer in her family.
C. Discontinue the drug because the results of recent trials have shown no cardiovascular benefit of hormone therapy and topical products are most effective in this particular situation.
D. Continue the drug because of the benefits on vasomotor symptoms and reducing the risk for osteoporosis.

24. A pharmacy student suggests that one of your postmenopausal patients with menopausal symptoms taking cyclic combined CEE-MPA should be switched to oral estradiol plus oral micronized progesterone based on recent Food and Drug Administration (FDA) labeling changes. Which one of the following is the best response?

A. This is not appropriate because the FDA requires labeling changes on all estrogen or estrogen-progestin products.
B. No change would be necessary because the FDA requires labeling changes for the continuous combined version of CEE-MPA but not the cyclic version of this combination.
C. This is not appropriate because the combination of estradiol and micronized progesterone are not indicated for cyclic use in postmenopausal women.
D. No change is necessary because the labeling changes only affect the transdermal estrogen and estrogen-progestin products.

25. Based on recent trials, which one of the following statements is true about hormone therapy?

A. Hormone therapy with combination estrogen-progestin led to a significant decrease in coronary events within the first year in women with a history of coronary artery disease.

Abbreviations

B. Hormone therapy with combination estrogen-progestin for 5 years decreased the incidence of coronary events in women with no history of coronary artery disease.
C. Women with no history of coronary artery disease who took combination estrogen-progestin for 5 years had a decreased risk of invasive breast cancer.
D. Women with no history of coronary artery disease who took combination estrogen-progestin for 5 years had an increased bone mineral density and decreased fracture risk.

Abbreviations