

DIALOGUES



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In This Issue

Management of Bleeding Disorders With Contraceptive Steroids

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Contraception for Women With Risk Factors for Venous and Arterial Thrombosis

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Management of Bleeding Disorders With Contraceptive Steroids

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Educational Objectives:

The health care provider should be able to:

- define different types of abnormal uterine bleeding
- evaluate women with abnormal uterine bleeding and implement differential diagnosis
- manage dysfunctional uterine bleeding with hormonal contraception

Definitions of abnormal uterine bleeding include the following major patterns: excessive blood loss (>80 mL) during menses or increased length (>7 days) of menses (menorrhagia); an increase in number of bleeding episodes (interval of ≤ 21 days between the start of successive menses; polymenorrhea); irregular bleeding episodes occurring at frequent intervals between menses (metrorrhagia); prolonged (≥ 7 days) bleeding at irregular, noncyclic intervals (menometrorrhagia); or extended (>35 days) intervals between menses (oligomenorrhea).¹⁻³ Dysfunctional uterine bleeding (DUB) is defined as abnormal uterine bleeding without an organic cause.^{1,4}

A US national study found that menstrual disorders, including abnormal uterine bleeding, were the reason for 18.5% of the 23.2 million ambulatory visits to clinician offices, hospital outpatient departments, and emergency departments for gynecologic conditions over a 2-year period (1995-1996).⁵ The presence of abnormal uterine bleeding is associated with 25% of gynecologic surgical procedures.⁴ It is estimated that excessive menstrual bleeding affects approximately 22% of all healthy menstruating women,^{6,7} and that DUB occurs in more than 10 million American women annually.⁶

Etiology

Organic Causes

The etiology of abnormal uterine bleeding falls into two general categories: organic causes and DUB (Table).^{1,4}

Dysfunctional Uterine Bleeding

DUB is a diagnosis of exclusion in the woman with no organic cause for abnormal uterine bleeding.^{1,8}

Definitions of DUB vary. It is estimated that about 90% of DUB is anovulatory and is most common at either end of the reproductive years, in the postmenarchal and premenopausal stages.^{1,8} Ovulatory abnormal uterine bleeding with no other organic cause (about 10% of women with DUB⁸) is associated with decreased endometrial vasoconstriction and vascular hemostatic plug formation⁹ and/or underlying imbalances in prostaglandin synthesis in the endometrium.⁹⁻¹¹

Differential Diagnosis

Correct diagnosis is critical to determine the appropriate treatment and/or management of the underlying cause of abnormal uterine bleeding. Evaluation is directed toward finding or excluding possible organic causes.

History

Medical history-taking should include medications, nonprescription drugs, herbs, supplements, and contraceptive methods, all of which may influence bleeding patterns; pregnancy history and complications; and history or possible symptoms of leiomyoma, endometrial polyps, polycystic ovarian syndrome (PCOS; eg, obesity, acne, hirsutism, acanthosis nigricans), and hypo/hyperthyroidism.^{1,4} While it is important to know whether the woman has had irregular bleeding for a long time, menstrual history-taking should focus on the current bleeding problem. The timing, nature of bleeding, precipitating factors, and associated symptoms (eg, pain, fever, changes in bladder or bowel function) should be evaluated.⁴ While subjective, a woman's report of passage of blood clots, flooding, and/or socially embarrassing bleeding is usually a fairly reliable indicator of excessive uterine bleeding.^{1,2} Important markers include deviation from an individual woman's previously established menstrual pattern, a sudden increase in use of two or more sanitary pads/tampons per day, menses lasting 3 or more days longer than usual, intermenstrual bleeding, and/or an interval between menses of 4 or more days fewer than usual.¹ Use of a menstrual calendar over a period of several months may help clarify the extent of the bleeding problem and determine whether bleeding is ovulatory or anovulatory.⁴

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Physical Examination

A careful physical examination of the external and internal genital tract is necessary to detect gross lower genital tract, uterine, and adnexal abnormalities.¹² A routine Pap test should be performed to detect cervical dysplasia.¹

In the majority of cases, a normal bimanual pelvic examination with a history suggestive of anovulation increases the likelihood of a diagnosis of DUB. In those women who are ovulating, sonohysterography is a useful technique to identify a submucous myoma or endometrial polyp (see below).¹³

Laboratory Testing

All women of reproductive age with abnormal uterine bleeding should have a pregnancy test and a complete blood count performed.¹⁴ In adolescents with heavy bleeding, women with a family history of a coagulopathy, and women of any age with easy bruising and nose and gum bleeding, coagulation screening and platelet measurement should be performed to detect or rule out coagulation disorders such as von Willebrand disease.²⁴ The most common hereditary bleeding disorder, von Willebrand disease is more prevalent than previously suspected¹⁹ and may cause abnormal bleeding, particularly in adolescents.² Clinicians should consider consulting a hematologist or the laboratory to determine which tests for diagnosis of von Willebrand disease are appropriate in a given situation since some functional tests may be altered by hormonal or other therapy.

Sometimes, additional laboratory tests may be indicated, such as serum ferritin to detect iron deficiency,² and/or a prothrombin time to detect liver disease (particularly in adolescents).³ Anovulatory women should have measurement of thyroid-stimulating hormone and prolactin.

Imaging Studies

Imaging technologies now provide the capability to detect a wide variety of uterine lesions effectively and conveniently. Pelvic sonography can detect lesions such as leiomyoma and endometrial polyps.^{3,14} Sonohysterography (ultrasound with saline infusion) has high sensitivity and specificity and is more accurate than transvaginal ultrasound alone for diagnosing intracavity lesions.^{3,15} This method clearly delineates the type and location of endometrial abnormalities, particularly polyps and submucous myoma.¹³ It is expected that sonohysterography will soon become the standard imaging method for evaluation of the endometrial cavity. Sonohysterography has been found to be as accurate as hysteroscopy for the diagnosis of endometrial polyps and submucous fibroids in premenopausal women.¹⁵

Histologic Evaluation

Controversy regarding whether to initially perform imaging studies or endometrial biopsy has not been resolved.¹⁶ Similarly, it is uncertain whether every woman with abnormal uterine bleeding should undergo endometrial biopsy. Endometrial biopsy should be performed in all women with abnormal uterine bleeding who are aged 35 or more and in younger women who have PCOS, as well as in women who are obese, and those who have a family history of

endometrial cancer, a long history of anovulatory bleeding, or bleeding unresponsive to treatment.^{4,17} The specificity of endometrial biopsy may be enhanced by hysteroscopy to eliminate blind sampling and subsequent failures to detect focal cancers.¹⁸ A variety of devices are available for in-office endometrial biopsy. Performance of dilatation and curettage (D & C) is not necessary to evaluate the cause of abnormal uterine bleeding. Most in-office biopsy devices provide as much information as standard D & C, which should be reserved for women with severe cervical stenosis, inadequate outpatient tissue sampling, or high suspicion of malignancy with negative office biopsy findings.⁴

Management

If abnormal uterine bleeding is found to result from reproductive tract disease, systemic disease, or iatrogenic causes, management and/or treatment should focus on ameliorating the underlying cause and the symptoms.² If, through exclusion of all other causes, DUB is diagnosed, the objectives of management are to control the bleeding, prevent recurrence, preserve fertility, and induce ovulation in anovulatory women who wish to conceive.¹⁰ In general, if DUB is present, medical treatment should be implemented before surgical options. Such surgical options, including various forms of endometrial ablation and hysterectomy, are useful when medical modalities have previously failed, but their use is beyond the scope of this article. While this discussion focuses on management with contraceptive steroids, other pharmacologic modalities are available (eg, antifibrinolytic agents, non-steroidal anti-inflammatory agents [NSAIDs], gonadotropin-releasing hormone [GnRH] agonists). Use of NSAIDs every 6 hours during the bleeding episode, alone or in combination with contraceptive steroids, has been found to be effective in reducing blood flow in most women with menorrhagia; one review of studies concludes that 75% of women treated with NSAIDs will have an average 30% reduction in menstrual blood loss (MBL).¹⁹

Combination Hormonal Methods

In women with DUB, combination estrogen-progestin hormonal contraceptive methods (combination oral contraceptives [COCs; eg, Alesse®, Levlen®, Lo/Ovral®], transdermal patch [ORTHO-EVRA®], vaginal ring [NuvaRing®]) are effective for cycle regulation, reduction of MBL, and prevention of endometrial hyperplasia. Estrogen stabilizes the endometrium immediately, minimizing irregular shedding and breakthrough bleeding.²⁰

A study of low-estrogen-dose (<50 mcg) COC (30 mcg ethinyl estradiol [EE]/150 mcg desogestrel) use in 20 young women found that MBL was reduced at 6 months by about 44% from pre-use baseline levels.²¹ Five of the women had baseline MBL of more than 80 mL; all were later found to have MBL of less than 80 mL. A randomized trial of various treatments for women with ovulatory menorrhagia found that a low-dose COC (30 mcg EE/150 mcg levonorgestrel [LNG]) significantly ($p < .001$) reduced MBL by 43% compared with a pre-use control cycle.²² In a randomized, placebo-controlled 84-day trial of a COC containing

Table. Etiology of Abnormal Uterine Bleeding

Organic Causes

Reproductive Tract Disease

- Complications of pregnancy
- Premalignancy
- Malignancy
- Infections
- Benign pelvic lesions (eg, submucosal uterine leiomyoma, endometrial polyps)

Systemic Disease

- Coagulation disorders (eg, thrombocytopenia, prothrombin deficiency, von Willebrand disease)
- Hypothyroidism
- Cirrhosis
- Polycystic ovarian syndrome

Iatrogenic Causes

- Exogenous steroids
- Foreign bodies
- Nonhormonal drugs (eg, tranquilizers, psychotropic agents, anticoagulants)

Dysfunctional Uterine Bleeding

Adapted with permission from Brenner¹

35 mcg EE and triphasic norgestimate (NGM; Ortho Tri-Cyclen®) among women with DUB, more than 80% of COC users had improvement in amount of bleeding significantly ($p < .001$) more than the placebo group, as assessed by investigators and participants.²³

Extended- and continuous-use regimens of COC, patch, and vaginal ring use may benefit some women with DUB, particularly those experiencing menorrhagia and/or anemia, by inducing short- or long-term amenorrhea to reduce the frequency of bleeding episodes. Studies of extended- or continuous-use COC regimens have found reductions in bleeding days and reductions in amount of bleeding compared with cyclic COC regimens, although these studies were not specifically designed to evaluate women with DUB.²⁴⁻²⁷ Intermenstrual bleeding and spotting persists or increases for several cycles in some women on extended- or continuous-use COC regimens, indicating that this approach may not be appropriate for all women with DUB.²⁴⁻²⁶

A clinical trial of extended use of the transdermal patch in healthy, regularly menstruating women resulted in fewer median bleeding days, bleeding episodes, and bleeding or spotting episodes as well as a greater incidence of amenorrhea during the 84-day study than did cyclic patch use.²⁸

In a randomized trial in healthy cycling women of four regimens (28-day, 49-day, 91-day, 364-day cycles) of vaginal ring use, the extended cycles resulted in fewer total days of bleeding, but many women experienced an increase in unscheduled spotting days compared with the 28-day cycle.²⁹

Progestin-Only Methods

Control of DUB with use of progestin-only methods is generally less successful than with use of combination hormonal methods. Intermenstrual bleeding/spotting is common immediately following initiation of use of progestin-only OCs,³⁰ and both irregular and frequent bleeding may occur for several months with other progestin-only methods before most women become amenorrheic. Nevertheless, oral medroxyprogesterone acetate (MPA; Provera®) 5 mg or 10 mg per day for the first 2 weeks of every month may help regulate cycles in women with anovulatory DUB.³ In women with ovulatory DUB, MPA is not as effective as in anovulatory women.³¹ Oral MPA or depot MPA (Depo-Provera®) can also be used continuously, and may be more effective than cyclic administration in treating ovulatory DUB by eventually producing amenorrhea.³¹ Norethindrone acetate (Aygestin®; available in 5 mg only) 2.5 mg to 10 mg per day for 5 to 10 days per month is an oral progestin-only alternative.³ Some clinicians have observed high rates of amenorrhea in women with DUB treated with daily norethindrone acetate.

The LNG-releasing intrauterine system (IUS; Mirena®) has been found in several randomized controlled trials to be an extremely effective, non-invasive method for reduction of MBL during treatment of menorrhagia

and DUB, with comparable outcomes and costs lower than endometrial resection or hysterectomy.³²⁻³⁶ Local administration of LNG to the endometrium causes epithelial atrophy, thus reducing MBL.³⁶ Like other progestin-only methods, the LNG-IUS may produce irregular bleeding during the first several months of use before the amount of blood loss decreases.^{32,33}

Special Factors

In women with acute uterine hemorrhage caused by DUB, tapered COC use can be administered. For acute nonemergency bleeding in women not at high risk for venous thromboembolism (VTE), three to four tablets of a monophasic COC can be given each day for 5 to 7 days; once the bleeding has satisfactorily decreased, the dosage is reduced to a daily regimen for 3 weeks, followed by discontinuation to allow withdrawal bleed.³¹ One of the combination hormonal methods can then be initiated as ongoing treatment for DUB. For acute nonemergency bleeding in women at high risk of VTE, progestin-only therapy can be utilized instead of estrogen-containing methods. Following endometrial biopsy, perimenopausal women with DUB who have no contraindications to hormone use can be treated with COCs or LNG-IUS, which may obviate the use of more invasive options. If medical therapy fails to ameliorate DUB, hysterectomy or endometrial ablation can be considered for women who have completed childbearing.¹⁷

Summary

The etiology of abnormal uterine bleeding includes organic causes and DUB. Correct diagnosis is critical to determine appropriate treatment and/or management of the underlying cause of abnormal bleeding. Medical history, menstrual history, and physical examination—supported when appropriate by laboratory testing, imaging studies, and histologic evaluation—are the basis for differential diagnosis.

Diagnosis of DUB is made by exclusion of all organic causes including reproductive tract lesions, systemic diseases, and iatrogenic causes. About 90% of DUB is anovulatory. The objectives of DUB management are to control the bleeding, prevent recurrence, preserve fertility, and induce ovulation in anovulatory women who wish to conceive. Medical modalities should be implemented before surgical options. Use of combination hormonal methods or progestin-only methods, including the LNG-IUS, has been proven to be effective in ameliorating DUB. The variety of available medical treatments facilitates appropriate selection of a management strategy to provide an individualized approach to effective and satisfactory improvement.

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Contraception for Women With Risk Factors for Venous and Arterial Thrombosis

Ronald T. Burkman, MD, and Philip D. Darney, MD, MSc

Educational Objectives:

The health care provider should be able to:

- identify the risk factors for venous and arterial thrombosis
- appropriately evaluate women for the presence of vascular risk factors
- determine appropriate contraceptive methods for women with increased risk for arterial and/or venous thrombosis

While the overall risk of cardiovascular disease (CVD) is very low in reproductive-age women,¹ risks of venous thrombosis are increased during pregnancy and the risk of arterial thrombosis is increased in women with risk factors for CVD; highly effective contraception is important for women at increased risk for both venous and arterial thrombosis. Selection of appropriate contraception for each woman depends to a great extent on her risk factor(s).

Arterial Thrombosis

Incidence Rates of Stroke and Myocardial Infarction (MI)

Among normotensive reproductive-age women who do not smoke or have diabetes, the incidence of arterial thrombotic events is extremely low but increases with age.¹ Age-specific baseline incidence rates of MI per 10,000 woman-years are 0.0014 at ages 20 to 24, 0.017 at ages 30 to 34, and 0.213 at ages 40 to 44. Incidence of stroke is higher but still very low: for ischemic stroke and hemorrhagic stroke, respectively, the baseline incidence rates per 10,000 woman-years are 0.060 and 0.127 at ages 20 to 24, 0.098 and 0.243 at ages 30 to 34, and 0.160 and 0.463 at ages 40 to 44.¹

Risk Factors for Arterial Thrombosis

Several factors increase the risks of arterial and/or venous thrombosis (Table 1).¹⁻²⁵

Cigarette smoking is a major risk factor for arterial thrombosis.^{1,26} Compared with nonsmoking, smoking in women has been found to increase absolute risks of MI 2 to 5 times,^{1,27,28} of ischemic stroke about 1.5 to 2 times,^{1,12,29-31} and of hemorrhagic stroke about 2 times.^{1,32,33}

Uncontrolled hypertension is also a risk factor for arterial thrombosis, particularly in women with preexisting vascular disease or those who are older than 35.^{1,34} Individuals with systolic blood pressure of 160 mm Hg or higher and/or diastolic blood pressure of 95 mm Hg or higher have a relative risk (RR) for stroke about 4 times greater than those with normal blood pressure.³⁵ The RR of MI is 5 to 10 times higher in women with a history of uncontrolled elevated blood pressure than in those with no such history.^{1,27,36}

Obesity is a modifiable risk factor for MI and other coronary heart disease.^{3,26,37} Abdominal obesity is an independent risk factor for ischemic stroke in all racial and ethnic groups, with an odds ratio (OR) about 3 times greater in the highest quartile of waist-to-hip ratio than in the lowest quartile.⁵ Obesity is also an underlying risk factor for atherosclerotic CVD associated with an increased incidence of other CVD risk factors (eg, hypertension, dyslipidemias).³⁸

Diabetes increases risk of stroke, with epidemiologic studies reporting RRs ranging from 1.8 to about 6 compared with people with normal glucose tolerance.¹² Between two thirds and three fourths of people with diabetes die of some form of CVD.³⁵

Among individuals with systemic lupus erythematosus (SLE), the lifetime prevalence of arterial and venous thrombosis is more than 10%.^{10,39,40} Thrombosis in SLE occurs because of hypercoagulability associated with antiphospholipid syndrome, premature atherosclerosis, and vasculitis.^{10,41} A leading cause of death in individuals with SLE is coronary heart disease.^{9,42}

Raised total serum cholesterol is a risk factor for MI in young women.¹ High levels of low-density lipoprotein (LDL) cholesterol and low levels of

high-density lipoprotein (HDL) cholesterol are associated with increased risk of coronary heart disease.⁴³⁻⁴⁶ Elevated fasting triglyceride levels increase risk of arterial disease only if levels of HDL cholesterol are low.⁴⁷ Familial combined hyperlipidemia and/or familial hypertriglyceridemia are risk factors for arterial CVD events and mortality.^{48,49}

Inherited thrombophilias (eg, factor V Leiden [FVL] mutation; prothrombin 20210 mutation; deficiencies of proteins C and S; and, possibly, methyl-ene-tetrahydrofolate reductase 677T variant) have been found to increase risk of stroke in individuals aged under 50 years.^{14,50} FVL and the prothrombin 20210A mutations have also been associated with an increased risk of MI in young women.^{13,51} In a meta-analysis of data from studies of more than 17,000 patients, FVL and prothrombin G20210A mutation were also found to modestly increase risk of all arterial ischemic events (ORs, 1.21, 1.32, respectively); however, the associations were more robust for women and in individuals aged less than 55.⁵²

Venous Thromboembolism (VTE)

Incidence Rates of VTE

The absolute risk of VTE is low in women of reproductive age. Among healthy women aged 14 to 45 who are not pregnant and not using hormones, the incidence of VTE is about 0.5 per 10,000 woman-years of use.^{2,53} The incidence of VTE rises with age, from 0.3 per 10,000 woman-years at

Table 1. Effects of Independent Risk Factors on Relative Risk of Arterial and Venous Thrombosis Compared With Absence of Risk Factors in Reproductive-Age Women

— = no effect; + = weak relative increase in risk; ++ = modest relative increase in risk; +++ = strong relative increase in risk

Risk Factor	MI	Stroke	VTE
Pregnancy	++ ¹	+++ ¹	+++ ²
Smoking	+++ ¹	+++ ¹	— ^{a,1}
Hypertension (uncontrolled)	+++ ¹	+++ ¹	— ^{a,1}
Obesity	+++ ^{3,4}	+++ ⁵	++ ⁶
Diabetes	+++ ⁷	+++ ⁷	— ⁸
SLE	+++ ⁹	+++ ¹⁰	+++ ¹¹
Dyslipidemias	+++ ¹	+ ¹²	+ ⁸
Inherited thrombophilia	++ ¹³	++ ¹⁴	+++ ¹⁵⁻¹⁸
Acquired thrombophilia	— ^{b,14}	+ ^{b,14}	+ ^{19,20}
Older age	+ ^{b,1}	+ ^{b,1}	+ ^{b,21}
Migraine with aura	—	+++ ²²	—
Combined hormonal contraception	— ^{b,1}	— ^{b,1}	+ ^{b,1,2}
Progestin-only contraception	— ^{b,23,24}	— ^{b,23,24}	— ^{b,23,24}
Family history of VTE without risk factors	+ ³	++ ¹²	++ ²¹

^aMajority of evidence indicates that smoking and hypertension are not independent risk factors for VTE¹; however, the findings of some studies are exceptions.^{8,25}

^bIn women with no other risk factors for cardiovascular disease.

MI=myocardial infarction; VTE=venous thrombosis and embolism; SLE=systemic lupus erythematosus.

ages 20 to 24 to 0.6 per 10,000 woman-years at ages 40 to 44.^{21,54} Among pregnant women, the risk of VTE is 6 per 10,000 pregnant woman-years.²

Risk Factors for VTE

For the most part, VTE is a multicausal disease in which several risk factors, both genetic and acquired, have to interact for thrombosis to occur (Table 1).¹⁹ The presence of any of a variety of factors increases VTE risk. Women with one or more of these characteristics may already be at increased risk for VTE; interaction of some of these factors with each other and/or with exogenous estrogen may multiply risk.^{55,56}

Inherited hypercoagulable conditions are present in a large proportion of individuals with VTE, including deficiencies of antithrombin, proteins C and S, FVL, and factor II G20210A.¹⁵⁻¹⁸ The risk of VTE is increased in women with homozygous or combined defects, particularly during pregnancy and the postpartum period.⁵⁷

Inherited thrombophilias, particularly the FVL mutation, often lead to activated protein C resistance (APCR).⁵⁸ APCR in individuals with VTE is most often (10% to 50% of cases) the result of FVL.¹⁵ In a 2004 US case-control study, the adjusted OR of VTE was 7.10 (confidence interval [CI] 2.33-21.61) among women with FVL aged 15 to 44 compared with that among women of similar ages without this mutation.⁵⁹

The G20210A prothrombin mutation is associated with elevated prothrombin levels.⁶⁰ When prothrombin levels were measured in women with VTE and in healthy women, women in the highest prothrombin quartile (>1.11 IU/mL) had an OR of VTE of 3.10 (CI, 1.73-5.55) compared with women in the lowest quartile (≤0.94 IU/mL).

Pooled analysis of data from eight case-control studies (2310 cases, 3204 controls) found that the ORs of VTE were 4.9 (CI 4.1-5.9) in individuals with FVL and 3.8 (CI 3.0-4.9) in those with the factor II G20210A mutation compared with noncarriers of these thrombophilic factors.⁶¹ Individuals with both mutations had an OR of VTE of 20 (CI 11.1-36.1).⁶¹

Genetic deficiencies of protein S, protein C, and ATIII produce a prothrombotic state that moderately increases risk of VTE.¹⁵ Taken together, these three abnormalities are found in only 5% to 15% of individuals with VTE.¹⁵ In a retrospective study, the incidences of VTE per woman-year were found to be 3.4% in women with ATIII deficiency, 6.9% in those with protein C deficiency, and 8.6% in those with protein S deficiency.⁶²

Although most APCR is associated with the presence of FVL,¹⁷ APCR may also develop as a result of such acquired conditions as pregnancy and SLE.²⁰ APCR in the absence of FVL independently increases the risk of VTE.^{20,63}

Individuals with antiphospholipid antibodies have an increased risk for VTE. A 2005 systematic literature review found that the ORs of VTE risk in the presence of anticardiolipin antibodies ranged up to 2.51; ORs of VTE risk in the presence of lupus anticoagulant ranged from 4.09 to 16.2.¹¹

Obesity (body mass index [BMI] ≥30 kg/m²) has been found to be an independent risk factor for VTE, particularly for pulmonary embolism (PE).^{6,8,25,35,64} Major surgery within the past 4 weeks is also a risk factor for VTE.⁵⁸ Because of the hypercoagulable state that follows pregnancy, the postpartum risk of VTE is 3- to 8-fold higher than that during pregnancy, which is itself 6- to 10-fold higher than in nonpregnant women of similar age.⁵⁷ Women with an inherited thrombophilia have an especially high risk of VTE during pregnancy and the puerperium.^{56,65}

The majority of studies indicate that smoking and hypertension, which are important risk factors for arterial disease, are not risk factors for VTE.¹

Evaluation

Clinical evaluation of women considering use of hormonal contraception who may have risk factors for CVD should begin with a complete personal and family history to determine any immediate personal or family history of MI, stroke, or VTE, as well as personal risk factors for CVD, including smoking, hypertension, obesity, diabetes, and SLE.^{1,54}

Routine screening for inherited or acquired thrombophilic factors prior to prescribing hormonal contraception is not recommended in asymptomatic women^{1,19,53,66} because most women with thrombophilias will never develop VTE, whether or not they use exogenous estrogen.⁶⁷ Furthermore, screening tests for coagulation disorders have poor positive predictive value for a clinical event and may exclude from hormonal contraceptive use many women who could safely benefit from their use.^{1,21,66}

Screening for FVL and, possibly, other hypercoagulable conditions should be considered only in women with a strong family history of CVD, particularly idiopathic VTE in a first-degree relative.^{21,54}

Contraceptive Selection for Women With Thrombotic Risk Factors

The availability of a wide variety of effective contraceptive methods allows women and their clinicians to select appropriate options for women with risk factors for CVD (Table 2).^{34,68}

Table 2. Contraceptive Selection for Women With Risk Factors for Cardiovascular Disease^{34,68}

yes=appropriate selection; no=alternative selections preferable

Risk Factor	Combination Hormonal Methods (COCs, patch, vaginal ring)	Progestin-Only Methods (POPs, DMPA)	Other (copper IUC, LNG-IUS)
Smoking	Yes, if age <35	Yes, any age	Yes, any age
Hypertension	Yes, if controlled, age <35, nonsmoker	Yes, if controlled	Yes, controlled/uncontrolled
Obesity	Yes; patch may be less effective in obese women	Yes	Yes
Diabetes with vascular disease	Contraindicated	Yes (POPs)/No (DMPA)	Yes
Diabetes without vascular disease	Yes, if age <35	Yes	Yes
SLE	No	Yes	Yes
Dyslipidemias	Contraindicated in severe hypercholesterolemia or hypertriglyceridemia	Yes	Yes
Known inherited thrombophilia	No	Yes	Yes
Acquired thrombophilia	No	Yes	Yes
Age ≥35	Yes*	Yes	Yes
Migraine without aura	Yes*	Yes	Yes
Migraine with aura	Contraindicated	Yes	Yes
Strong family history of MI, stroke, VTE	Consider hypercoagulability testing: if positive, no; if negative, yes	Yes	Yes
Multiple CVD risk factors	No	Yes	Yes

*In the absence of other risk factors for CVD.

COCs=combination oral contraceptives; POPs=progestin-only oral contraceptives; DMPA=depot medroxyprogesterone acetate; IUC=intrauterine contraception; IUS=intrauterine system; LNG=levonorgestrel; SLE=systemic lupus erythematosus; MI=myocardial infarction; VTE=venous thrombosis and embolism; CVD=cardiovascular disease.

Combination Hormonal Methods

Combination hormonal methods, containing both estrogen and progestin, include combination oral contraceptives (COCs; eg, Estrostep®, Mircette®, Loestrin®), the transdermal patch (ORTHO EVRA®), and the vaginal ring (NuvaRing®). Although exogenous estrogen produces thrombophilic effects,

Summary

Among normotensive, nonsmoking, reproductive-age women without risk factors for CVD, the incidence of arterial and venous thrombotic events is extremely low. Although the risk of CVD is small even among women with risk factors, highly effective contraception is important for these women because risks of arterial or venous thrombosis are increased during pregnancy. Selection of appropriate contraception for each woman depends largely on her risk factor(s).

The vast majority of the evidence shows that use of combination hormonal contraceptives (COCs, patch, ring) does not increase risk of stroke or MI in reproductive-age, normotensive, nonsmoking women with no other risk factors for CVD. Because use of combination hormonal contraception in women older than 35 who smoke increases the risk of MI and hemorrhagic stroke, smokers older than 35 should not use these methods. Although use of COCs increases the risk of VTE 2 to 4 times the rate of 0.5 case per 10,000 woman-years among nonpregnant reproductive-age women not using COCs, the risk of VTE attributable to COC use is only an additional 2 to 3 cases per 10,000 woman-years of use. Inherited coagulation defects independently increase risk for VTE, and use of estrogen-containing contraceptives further increases this risk; however, routine screening for such defects before prescribing combination hormonal contraception is not recommended because few women with these conditions will experience VTE whether or not they use estrogen.

For women with certain CVD risk factors, use of estrogen-containing contraception should be avoided to prevent an increased risk of thrombosis (Table 2^{34,68}). Progestin-only and intrauterine contraceptive methods are appropriate alternatives for such women.

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(continued on page 8)

(see "Thrombophilic Effects of Estrogens and Progestins," page 7) the vast majority of the evidence indicates that use of estrogen-containing contraceptive methods does not increase risk of stroke or MI in reproductive-age, normotensive, nonsmoking women with no other risk factors for CVD.^{1,69-72}

A recent meta-analysis of studies of COC use and arterial disease found the summary ORs for current COC use to be 1.84 (CI 1.38-2.44) for MI, and 2.12 (CI 1.56-2.86) for ischemic stroke (no eligible studies included hemorrhagic stroke).⁷³ Although these risk estimates are somewhat higher than those in other studies, the risk attributable to COC use is still very small, about two cases per 10,000 woman-years. Even a high RR of a rare condition remains a very small absolute risk, so the low risk estimate in this meta-analysis is not worrisome. Furthermore, most studies included in the meta-analysis were from Europe, where more women who smoke or have high blood pressure are prescribed COCs than in the United States.^{72,73} The two large US studies included in the meta-analysis yielded lower summary ORs for COC use compared with nonuse, which were not significantly increased for stroke or MI (ischemic stroke, OR 0.52, CI 0.27-1.00; hemorrhagic stroke OR 0.91, CI 0.43-1.93; MI, OR 1.3, CI 0.8-2.2).^{69,74}

Studies have found an adverse and synergistic interaction between COC use and heavy smoking for increasing risk of MI and hemorrhagic stroke.^{69,72,74}

Use of COCs has been found to increase risk of VTE 2 to 4 times the baseline rate of less than one case per 10,000 woman-years in nonpregnant reproductive-age women not using COCs.^{2,59,64} The absolute risk of VTE with COC use (3 to 4 cases per 10,000 woman-years of use) and the excess risk attributable to COC use (additional 2 to 3 cases per 10,000 woman-years) are low and half the risk attributable to pregnancy.² New product labeling for the transdermal patch states that the pharmacokinetic (PK) profile for the contraceptive patch is different from the PK profile for COCs, as the patch has higher steady state concentrations and lower peak concentrations.⁷⁵ Area under the curve (AUC) and average concentration at steady state for ethinyl estradiol (EE) are approximately 60% higher in women using the contraceptive patch compared with women using a COC containing 35 mcg EE. In contrast, peak concentrations for EE are approximately 25% lower in women using the contraceptive patch. In general, increased estrogen exposure may increase the risk of adverse events. However, the labeling states, it is not known whether there are changes in the risk of serious adverse events based on the differences in PK profile between women using the contraceptive patch compared with women using COCs containing 35 mcg of EE. (See also "Thrombophilic Effects of Estrogens and Progestins," page 7.)

In women with FVL, use of COCs has been found to further increase risk of VTE (OR 10.25, CI 5.69-18.45) compared with nonusers with no thrombophilic mutations.⁶¹ In women with the factor II G20210A mutation using COCs, the OR of VTE was found to be 7.14 (CI 3.39-15.04).⁶¹

Absolute and Relative Contraindications

Because of these known risk factors for CVD, product labeling for combination hormonal methods *absolutely contraindicates* their use in women with current or past thrombophlebitis or thromboembolic disorders, current or past cerebral vascular or coronary heart disease, severe hypertension, diabetes with vascular involvement, or migraine with aura, and smoking over age 35.⁷⁵⁻⁷⁸ Product labeling also states that smoking increases the risk of serious CVD side effects with COC, patch, and ring use and that risk increases with age and heavy smoking. *Relative contraindications* for these agents include diabetes without vascular disease in women aged more than 35, severe hypercholesterolemia or hypertriglyceridemia, and hypertension with comorbidities.³⁴

Other Contraceptive Methods

Studies of oral and injectable progestin-only contraception (progestin-only OCs [POPs], depot medroxyprogesterone acetate [DMPA; Depo-Provera®]) have found no significant changes in overall risks of MI, stroke, or VTE in women without risk factors for CVD compared with nonusers.^{23,24} Users of POPs and DMPA with a history of hypertension have a substantially increased risk of stroke compared with nonusers of hormonal contraception with no such history, but the number of cases was small.²³ These methods are appropriate options for women with CVD risk factors. The copper intrauterine contraceptive (IUC; ParaGard®), and the levonorgestrel-releasing intrauterine system (LNG-IUS; Mirena®) are also appropriate options for women with CVD risk factors (Table 2).

Thrombophilic Effects of Estrogens and Progestins

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Venous thromboembolism (VTE) is a term indicating the presence of either deep venous thrombosis (DVT) and/or pulmonary embolism (PE).¹ The most serious complication of venous thrombosis is PE, with an in-hospital case-fatality rate of 23%.² Superficial thrombophlebitis may be associated with an asymptomatic DVT. Thrombosis affecting the deep veins of the leg is mostly limited to the calf veins, which are usually small and rarely associated with PE.³ Some calf vein thrombi (about 20%^{1,3}) extend into the popliteal vein and beyond and may be associated with a 50% risk of PE.^{1,3}

Effects of Contraceptive Steroids

Orally ingested ethinyl estradiol (EE), the estrogenic component of combination oral contraceptives (COCs; eg, Brevicon®, Norinyl®, Yasmin®), is metabolized slowly and produces thrombophilic effects by altering hepatic synthesis of factors involved in the process of coagulation and fibrinolysis.³⁻⁶ Slight increases in thrombin formation are usually offset by increased fibrinolysis. The thrombophilic effects are directly related to the dose of EE in the COC.^{3,5,7,8} In most women with no other risk factors for thrombosis (see "Contraception for Women With Risk Factors for Venous and Arterial Thrombosis," page 4), the thrombophilic effects of COC use are modest, with values of most factors involved in the coagulation process remaining within normal limits.⁹ EE administered transdermally (patch; ORTHO-EVRA®) or vaginally (NuvaRing®) is also metabolized slowly. The pharmacokinetic (PK) profile for the transdermal patch is different from the PK profile for COCs, as the patch has higher steady state concentrations and lower peak concentrations.¹⁰ Area under the curve (AUC) and average concentration at steady state for EE are approximately 60% higher in women using the contraceptive patch compared with women using a COC containing 35 mcg EE. In contrast, peak concentrations for EE are approximately 25% lower in women using the contraceptive patch. In general, increased estrogen exposure may increase the risk of adverse events. However, new patch labeling states, it is not known whether there are changes in the risk of serious adverse events based on the differences in PK profile between women using the contraceptive patch compared with women using COCs containing 35 mcg of EE.¹⁰

Most evidence indicates that progestins do not alter coagulation factors, and that the increased risk of VTE with COCs is related only to the thrombophilic effects of the estrogen component.¹¹ Contraceptives containing

progestins without estrogen do not increase hepatic synthesis of coagulation proteins and have been found not to significantly increase the risk of VTE.^{12,13} However, product labeling for combination hormonal contraceptives containing desogestrel or etonogestrel (active metabolite of desogestrel), which is present in the vaginal ring, states that several but not all studies have found a twofold increased risk of VTE with COCs containing desogestrel and gestodene (not available in the United States) compared with those containing levonorgestrel.^{14,15}

Rates of VTE in Reproductive-Age Women

Baseline incidences of VTE morbidity and mortality are very low. Among women aged 14 to 45 without exposure to either COCs or pregnancy, the incidence of VTE is about 0.5 per 10,000 woman-years.^{8,11} The risk of VTE increases with increasing age and increased body mass index (obesity); both are independent risk factors for VTE.¹⁶⁻¹⁸ The incidence of mortality in reproductive-age women (15 to 44) from VTE is 1 per 100 cases.¹⁹ Among pregnant women, VTE incidence is 6 per 10,000 woman-years.^{8,20} In US pregnancy-related mortality surveillance data from 1991 to 1999, embolism was the leading cause of pregnancy-related deaths (19.6%).²¹

Risks of VTE With Combination Hormonal Contraception Use

Current use of low-estrogen-dose (≤ 35 mcg) COCs increases VTE risk 2 to 4 times the baseline rate, from 1 to about 3.7 per 10,000 woman-years.^{3,8,22,23} Thus, the absolute risk of VTE with COC use is low: 3 to 4 cases per 10,000 woman-years of use. The excess risk attributable to COC use is an additional 2 to 3 cases per 10,000 woman-years. The risk of VTE with pregnancy is about six times the baseline rate, twice that associated with COC use.

Recent media reports have suggested that the risk of VTE is increased with transdermal patch use compared with COC use. Some reports stated that 44 cases of VTE occurred between May 1, 2002, and May 1, 2003.^{24,25} However, the reported cases have not been documented to be associated with patch use alone instead of other risk factors, and no definitive number of woman-years of patch use has been confirmed to provide an incidence rate. Therefore, epidemiologic analysis to determine risk of VTE by dividing the number of documented cases (numerator) by the number of individuals exposed to the patch per unit of time (denominator) has not yet been possible. Even if all 44 reported cases were documented, a crude estimate utilizing the total number of prescriptions for the patch during the period suggests that the relative risk of VTE with patch use would be about 4 cases per 10,000 woman-years of patch use, comparable to the risk of VTE with COC use.

Without case documentation and determination of a denominator, there is no accurate method to determine the relative risk of VTE with contraceptive patch use. Clinicians can tell women that there are no epidemiologic data demonstrating a greater increased risk of VTE with the patch than with COCs. (For additional discussion of this issue, see *Dialogues in Contraception*, Vol. 8, No. 7.)

Summary

Exogenous estrogen produces thrombophilic effects that can increase VTE risk in some women. Most evidence indicates that progestins have no significant impact on coagulation factors. The risk of VTE in users of combination hormonal contraceptive methods is increased compared with nonusers, but the absolute risk remains very low and half that associated with pregnancy.

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