Hormonal Contraception and Thrombotic Risk: A Multidisciplinary Approach

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KEY WORDS
contraception, thrombosis, thrombophilia, hormone

ABBREVIATIONS
DUB—dysfunctional uterine bleeding
HRT—hormone-replacement therapy
VTE—venous thromboembolic event
COC—combined oral contraceptive
CI—confidence interval
EE—ethinyl estradiol

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abstract

Heightened publicity about hormonal contraception and thrombosis risk and the publication of new guidelines by the World Health Organization in 2009 and the Centers for Disease Control and Prevention in 2010 addressing this complex issue have led to multidisciplinary discussions on the special issues of adolescents cared for at our pediatric hospital. In this review of the literature and new guidelines, we have outlined our approach to the complex patients referred to our center. The relative risk of thrombosis on combined oral contraception is three- to fivefold, whereas the absolute risk for a healthy adolescent on this therapy is only 0.05% per year. This thrombotic risk is affected by estrogen dose, type of progestin, mechanism of delivery, and length of therapy. Oral progestin-only contraceptives and transdermal estradiol used for hormone replacement carry minimal or no thrombotic risk. Transdermal, vaginal, or intrauterine contraceptives and injectable progestins need further study. A personal history of thrombosis, persistent or inherited thrombophilia, and numerous lifestyle choices also influence thrombotic risk. In this summary of one hospital's approach to hormone therapies and thrombosis risk, we review relative-risk data and discuss the application of absolute risk to individual patient counseling. We outline our approach to challenging patients with a history of thrombosis, known thrombophilia, current anticoagulation, or family history of thrombosis or thrombophilia. Our multidisciplinary group has found that knowledge of the guidelines and individualized management plans have been particularly useful for informing discussions about hormonal and nonhormonal options across varied indications. *Pediatrics* 2011;127:347–357

Hormonal contraceptives are frequently prescribed in the adolescent age group for a variety of indications including contraception, dysmenorrhea, endometriosis, ovarian cyst suppression, polycystic ovary syndrome, dysfunctional uterine bleeding (DUB), and hormone-replacement therapy (HRT) for primary ovarian insufficiency. For example, among the 42% of adolescent girls 15 to 19 years of age who have had sexual intercourse (2006–2008 National Survey of Family Growth), 55% have used oral contraceptives, 10.5% the contraceptive patch, 7% the vaginal ring, and 17% injectable hormones.[1] Similarly, at most recent intercourse, 84% of teenagers had used some method of contraception that included oral contraceptive pills (30.5%) and other hormonal methods such as the patch, ring, injectable medications, or an implant (10.4%). In addition, many young women rely on these medications for indications other than contraception. In general, these commonly used hormonal methods are well tolerated, but given their frequent use,[1] even rare adverse effects and complications have gen-

erated significant public concern. No potential adverse effect has garnered more attention recently than venous thromboembolic events (VTEs).

The association between thrombosis and oral contraceptives that contain estrogen and progestin was first noted in the 1960s,[2] soon after these products became widely available. As the mechanisms of blood coagulation became clearer and large registries were established, numerous studies evaluated thrombotic risk attributed to estrogen in hormonal contraception or replacement therapy. In 1995, several articles reported an increased risk of VTEs with combined oral contraceptives (COCs), particularly those that contain the progestin desogestrel, and also highlighted the risks associated with the factor V Leiden mutation.[3–6] The publicity generated by these articles was associated with a subsequent increase in pregnancies, presumably attributable to a decrease in oral contraceptive use.[7] Subsequently, concern was raised about whether the transdermal contraceptive patch Ortho Evra (Ortho-McNeil-Janssen Pharmaceuticals, Raritan, NJ) conferred a higher risk of VTE, although conflicting data have been published.[8] Recently, the results of 2 studies suggested an increased relative risk of VTEs when using COCs that contain the progestins drospirenone and desogestrel compared with other COCs.[9,10] Intense media scrutiny of the potential VTE risk of drospirenone-containing COCs in particular (eg, Yaz/Yasmin [Bayer HealthCare Pharmaceuticals, Berkeley, CA]) has affected litigation, advertising, and patient-provider discussions.

Faced with complex patients whose clinical problems are often not addressed by current data or guidelines, we have delineated an approach to these challenging patient decisions. This review represents the approach of a multidisciplinary team of adolescent medicine, gynecology, endocrinology, and hemostasis/thrombosis consultants at a major pediatric referral hospital.

MECHANISMS OF VENOUS THROMBOSIS

Virchow's triad refers to 3 mechanisms that increase thrombotic risk: endothelial disruption; venous stasis; and procoagulant changes in blood proteins. Endothelial disruption occurs frequently with catheter insertion and also with trauma, surgery, burns, and toxins. Venous stasis may result from immobilization (orthopedic casting, prolonged travel), external compression (tumor, pregnancy), or cardiac conditions (heart failure, atrial fibrillation, or other arrhythmias). In addition, numerous alterations of blood proteins promote venous thrombosis, and fall into 1 of 3 categories: increased procoagulants; decreased anticoagulants; and decreased fibrinolytics.

HORMONE-INDUCED THROMBOTIC STATE

Estrogen is associated with numerous prothrombotic alterations in proteins involved in coagulation. COC users have several procoagulant changes in blood proteins, including increased levels of factors II, VII, VIII, and X and fibrinogen, decreased levels of antithrombin and protein S,[11] and acquired resistance to activated protein C.[12] First-pass hepatic metabolism of oral estrogen leads to increased hepatic synthesis of factor VII, factor X, and fibrinogen.[13] Similar prothrombotic changes to circulating coagulation proteins occur in mice receiving estradiol, which is mediated through estrogen receptor α.[14] In contrast, estrogen use may favor fibrinolysis through decreased plasminogen activator inhibitor-1 and increased plasminogen levels.[15]

Although estrogen was originally thought to be the only contributor to COC-induced thrombosis, certain progestins also seem to have important effects. Activated protein C resistance (assessed as a biochemical assay in vitro) is higher in COCs with levonorgestrel than those with desogestrel and may also be affected by first-pass hepatic metabolism.[13] Women who take COCs with desogestrel have increased procoagulant levels (factors VII, VIII, and X) and decreased anticoagulant levels (protein S and antithrombin) compared with nonusers.[11]

The risks of hormonal preparations related to VTEs vary depending on the dose of estrogen, type of progestin, age, family history, presence of other thrombophilia, and other factors. The relative risk for thrombosis in patients who take COCs is three- to fivefold higher compared with that of nonusers.[10] The risk when thrombophilia and COCs are combined can be much higher (eg, up to 35 times for factor V Leiden heterozygotes who use COCs[16]). Although VTEs may occur at any time, thrombotic risk is maximal during the first 12 months (particularly first 3 months) of using COCs,[9] which is attributed to exposure to a new risk factor, especially if other risk factors are also present. Compared with nonusers, the relative risk of VTEs for COC users for the first year was 7.0 (95% confidence interval [CI]: 5.1–9.6); for 1 to 5 years, 3.6 (95% CI: 2.7–4.8); and for >5 years, 3.1 (95% CI: 2.5–3.8).[17] Thrombotic risk is also increased with high-estrogen COCs relative to standard and low-dose estrogen formulations. Except for the COC with estradiol valerate approved in 2010, the vast majority of COCs prescribed contain 20 to 35 μg of ethinyl estradiol (EE); there are still a few COCs with 50 μg of EE or 50 μg of mestranol (which is converted to ~35 μg of EE). Although continually in flux, an extensive listing of

currently available formulations is offered in a recent text.[18] Using 30-μg EE/levonorgestrel COCs as the reference standard, the odds ratio was 1.1 (95% CI: 0.4–3.1) for 20-μg COCs and 2.2 (95% CI: 1.3–3.7) for 50-μg COCs.[10]

Most of the progestins used in COCs are 19-nortestosterone derivatives with varying estrogenic, antiestrogenic, progestational, antiandrogenic, and androgenic properties. These progestins include norethindrone, norethindrone acetate, ethynodiol diacetate, norgestrel, levonorgestrel, desogestrel, norgestimate, dienogest, and gestodene (not available in the United States). Norgestrel is a racemic mixture of dextronorgestrel and levonorgestrel with the levonorgestrel being the active isomer (thus, 0.3 mg of norgestrel can be considered equivalent to 0.15 mg of levonorgestrel). Drospirenone is a synthetic progestin chemically related to 21-carbon 17α-spironolactone with antimineralocorticoid and antiandrogenic activity. The results of 2 recent studies have highlighted epidemiologic data indicating that progestins such as levonorgestrel, norethindrone, and likely norgestimate convey lower thrombotic risk than desogestrel and drospirenone (Table 1). Desogestrel had been reported in the mid 1990s to confer a slightly higher risk of VTEs than other COCs, although the authors of 2 recent studies of drospirenone reported no increased risk relative to other COCs.[19,20] Gestodene, a progestin that is unavailable in the United States, has also been previously implicated to convey an increased VTE risk compared with other COCs, although recent data have suggested no increased risk in current users.[21]

TABLE 1 Risks of Thrombosis According to Progestin

Progestin	Rate Ratio of Thrombosis Compared With Levonorgestrel
Levonorgestrel	1.00
Norethisterone (norethindrone)	0.98 (0.71–1.37)
Norgestimate	1.19 (0.96–1.47)
Drospirenone	1.64 (1.27–2.10)
Desogestrel	1.82 (1.49–2.22)
Gestodene[a]	1.86 (1.59–2.18)
Cyproterone acetate[a]	1.88 (1.47–2.42)

All data are from preparations with 30 to 40 μg of estrogen.

[a] Not available in the United States.

Adapted from Lidegaard O, Lokkegaard E, Svendsen AL, Agger C. *BMJ*. 2009;339:b2890.

Data from studies of the Ortho Evra patch have also been conflicting. The thrombotic risk was reportedly higher than that of COCs, presumably because of greater total estrogen delivery despite lower peak levels,[22] and these data led to a change in the package insert. However, subsequent studies found no increased risk compared with 35-μg EE/norgestimate COCs[23,24] and levonorgestrel COCs[8] and raised questions about the reference groups used in previous studies. The authors of 2 recent updates came to different conclusions; one demonstrated no increased risk overall[25] and another showed a twofold increased risk,[26] which leaves the clinician to convey the ongoing uncertainty about relative risk compared with COCs while also highlighting the reassuring low absolute risk. Early data suggest that transvaginal[27] or intrauterine[9] hormone-delivery systems may confer less thrombotic risk than oral formulations, but definitive data have not yet been reported.

Finally, users of progestin-only pills have a thrombotic risk similar to that of nonusers (adjusted rate ratio: 0.59 [95% CI: 0.33–1.04] for 0.35-mg norethindrone and 1.1 [95% CI: 0.35–3.41] for 75-μg desogestrel [not available in the United States]).[9] Studies of injectable progestins have generally revealed no increased risk, although the authors of 1 recent study reported an odds ratio of 3.6 (95% CI: 1.8–7.1) for thrombosis.[28] However, whether injectable progestins are risk factors independent of BMI was not reported but is particularly salient, because weight gain is common among depot medroxyprogesterone acetate users.

HRT, which includes other oral or transdermal estrogen/progestin combinations, is prescribed for adolescents with conditions such as hypothalamic amenorrhea and primary ovarian insufficiency. The goals of HRT in adolescents are to induce normal breast development and menses and promote acquisition of normal bone mass. Most studies of VTE risk with HRT have involved the use of oral conjugated estrogens and medroxyprogesterone in perimenopausal women and have demonstrated a low absolute risk of VTEs despite the older age and other risks in that population. Similar to hormonal contraception, increased VTE risk is most evident during the first year of treatment[29] and is compounded by other prothrombotic risk factors.[30] In contrast, transdermal β-estradiol preparations (Vivelle dot [Novogyne Pharmaceuticals, East Hanover, NJ], Estraderm [Novartis, East Hanover, NJ], Climara [Bayer HealthCare Pharmaceuticals]), which provide physiologic levels of estrogen specifically for estrogen replacement and are qualitatively distinct from the ethinyl estrogen used in contraceptives, seem to confer no increased risk of VTEs,[31–33] perhaps because transdermal estradiol replacement avoids the procoagulant effects of first-pass hepatic metabolism.

INHERITED THROMBOPHILIA

Thrombophilia refers to factors predisposing to thrombosis and may be acquired or inherited. Thrombosis is a multifactorial disease that includes environmental, anatomic, and genetic influences. Although more than 2 dozen genes have been described as contributing minor risks of thrombo-

TABLE 2 Comparison of Hereditary Thrombophilias

Thrombophilia	General Prevalence, %	First VTE Prevalence, %	Relative Risk of First VTE	Annual Incidence of VTE, %
Factor V R506Q (FVL)	3–7	12–20	4.3	0.19–0.67
Factor II G20210A (PGM)	1–3	3–8	1.9	0.13
Combined FVL/PGM	0.1	—	32.4	0.57
Protein C deficiency	0.02–0.05	2–5	11.3	1–2
Protein S deficiency	0.01–1	1–3	32.4	1–2
Antithrombin deficiency	0.03	1–2	17.5	1.2

Data provided are for heterozygous deficiencies. Homozygous deficiencies carry significantly higher thrombotic risk but are too rare to be detected in population surveys. Prevalence data are as reported in white adults. FVL indicates factor V Leiden; PGM, prothrombin gene mutation G20210A.

Adapted from Heit JA. Thrombophilia: Clinical and laboratory assessment and management. In: Kitchens CS, Alving BM, Kessler CM, eds. *Consultative Hemostasis and Thrombosis.* 2nd ed. Philadelphia, PA: Saunders; 2007:213–244.

sis, a small number of genes account for the majority of known inherited thrombophilias.

Approximately 60% of inherited thrombophilia is currently explained by known genes (Table 2). Factor V Leiden is a point mutation (R506Q) in coagulation factor V that increases thrombin generation through resistance to proteolytic cleavage by activated protein C.[34] Data from population studies are consistent with a founder mutation in the eastern Mediterranean, where carrier rates are ≥14%.[35] Inherited activated protein C resistance is not explained by factor V R506Q in 5% of cases. A messenger RNA–stabilizing mutation in the 3′-untranslated region of factor II (prothrombin G20210A) is prothrombotic by increasing plasma prothrombin levels up to 30%.[36] Antithrombin is a serine protease that inactivates thrombin and also coagulation factors IXa, Xa, XIa, XIIa, and plasmin. Antithrombin activity increases by 2 to 3 logs when bound to heparin[37] (whether pharmacologic or endothelial). Protein C is a vitamin K–dependent serine protease activated by an endothelial thrombin/thrombomodulin complex.[38] Activated protein C inactivates the active isoforms of factors V and VIII. Protein S is a vitamin K–dependent cofactor required for activated protein C and tissue factor pathway inhibitor anticoagulant activity. Genetic deficiencies of anticoagulants antithrombin, protein C, or protein S are 10 to 100-fold less common than factor V Leiden or prothrombin gene mutation, although each confers significant thrombotic risk. Deficiencies in these anticoagulants are far more commonly acquired than inherited. The large number of unexplained cases of hereditary thrombosis has inspired a recent surge in genome-wide association studies. From these studies, multiple new gene polymorphisms, often common and conferring modest thrombotic risk, have been reported, but current data are insufficient to use in clinical decision-making.

ACQUIRED THROMBOPHILIA

Antiphospholipid antibodies refer to autoimmune antibodies associated with thrombotic risk. These antibodies include lupus anticoagulants, anticardiolipin antibodies, and anti-β2-glycoprotein 1 antibodies. Patients with chronic inflammatory conditions may develop persistent antiphospholipid antibodies (>12 weeks) and significant thrombotic risk. Given the numerous diagnostic tests available and complex literature on this topic, expert consensus guidelines for persistent antiphospholipid antibodies have been developed.[39]

Significant elevation of serum or urine homocysteine levels is prothrombotic in rare patients with homocystinuria.[40] The vast majority of people with an elevated homocysteine level, however, have dietary (eg, folate or vitamin B_{12} deficiency), medication-related (eg, methotrexate), or common genetic causes that are not independently prothrombotic in the absence of an elevated homocysteine level. For example, a polymorphism in the methyltetrahydrofolate reductase gene (thermolabile C677T) is common (up to 50% heterozygous and 30% homozygous, depending on ethnicity[41]) but is unrelated to thrombotic risk even with mildly elevated homocysteine levels.[42] Furthermore, homocysteine-lowering with vitamin B supplementation does not affect arterial[43,44] or venous[45,46] thrombosis rates.

ABSOLUTE RISK OF THROMBOSIS

Most studies of thrombotic risk have used relative risk, hazard ratio, or odds ratio calculations. However, for clinical decision-making, absolute thrombotic risk is much more valuable; one must take into account the age-dependent incidence of thrombosis multiplied by assessed relative risks. The incidence of thrombosis for adolescents (1–10 per 100 000 per year) and women of childbearing age (10–46 per 100 000 per year[16,47]) is low compared with perimenopausal women considering HRT (83–123 per 100 000 per year[48]). When comparing these incidence statistics to the carrier rates in white women of common inherited thrombophilias (at least 7%), it is clear that the vast majority of patients with thrombophilia will not have thrombotic complications on COCs.

As an example, a 17-year-old woman with a baseline risk of thrombosis of 1 to 10 per 100 000 per year would have a fivefold increased relative risk on COCs, which yields an absolute risk of 5 to 50 per 100 000 per year (up to 0.05% per year). If she is also a carrier for factor V Leiden, she would have a 35-times increased relative risk, but her absolute risk would remain low at 350

per 100 000 per year (0.35%/year). It should be noted that the incidence of VTEs rises ~10-fold with each 20 years of age and plateaus at ~75 years of age.[48] As cumulative absolute risk of VTEs increases, less-prothrombotic contraceptive options should be chosen.

Another important issue is the approach to a young woman with a positive family history of thrombosis. Whenever possible, it is recommended to evaluate the affected family member for thrombophilia and not an unaffected healthy patient. If the event occurred before the mid-1990s, factor V Leiden and the prothrombin gene mutation were not yet discovered and, therefore, likely not yet evaluated.

The thrombotic risk from COCs (3–5 times relative risk)[10] is often weighed against the thrombotic risk of unplanned pregnancy and the puerperium (4.3–10 times relative risk).[47,49] This risk is significant; venous thromboembolism is the leading cause of maternal mortality in the United States.[50] Thus, alternative means of contraception are favored for patients at high risk of thrombosis, whereas some indications (eg, severe DUB) for COCs may favor their use despite small increases in absolute thrombotic risk.

OTHER PROTHROMBOTIC RISK FACTORS

The risk of thrombosis while using COCs may be modified by several other prothrombotic risk factors. Most VTEs involve a combination of multiple contributory risk factors.[51] Given the variable and unpredictable nature of many of these risk factors, a rational decision-making process that takes into consideration their prothrombotic influence is important. Table 3 summarizes risk estimates in adults for common prothrombotic risk factors alone and in combination with COCs and illustrates that the thrombotic risk in combination with COCs is the same as or greater than the product of individual risks. In addition, some common acquired risk factors (eg, obesity and/or travel) rival or surpass the thrombotic risk from some inherited thrombophilias.

Both air and land travel increase thrombotic risk.[52] The prothrombotic mechanisms during air travel include immobility and venous stasis, dehydration, and hypobaric hypoxia.[53,54] Although risk is generally greatest for travel of >6 to 8 hours, every additional 2 hours of travel confers an 18% increase in risk.[55] The increased risk of thrombosis caused by trauma and surgery is attributed to endothelial disruption exposing tissue factor, relative venous stasis with immobilization, and alterations in coagulation proteins.[56,57] Smoking and obesity are also well-established prothrombotic risk factors.[58–61]

Hypercoagulability in malignancy is related to a variety of factors including indwelling lines, chemotherapy, inflammation, release of tissue factor–bearing microparticles from some cancers,[56,59] and external venous compression with resultant venous stasis.[62] Persistent antiphospholipid antibodies, usually associated with chronic inflammatory disorders including systemic lupus erythematosus, are also associated with increased risk of VTEs.[63] Other acquired prothrombotic conditions include increasing age, indwelling catheters, congestive heart failure, inflammatory bowel disease, nephrotic syndrome, hyperviscosity (eg, dehydration or malignant gammopathies), myeloproliferative disorders, and paroxysmal nocturnal hemoglobinuria.

COMPARISON OF GUIDELINES

Guidelines for the use of combined hormonal contraceptives in specific clinical situations have been promulgated by multiple groups (Table 4). The World Health Organization's *Medical Eligibility Criteria for Contraceptive Use*[64] are the most commonly referenced. In addition, the Faculty of Sexual & Reproductive Healthcare of the Royal College of Obstetricians and Gynaecologists in the United Kingdom has developed the *United Kingdom Medical Eligibility Criteria for Contraceptive Use*.[65] In the United States, the

TABLE 3 Risk Estimates for Several Common Prothrombotic Risk Factors and Prevention Strategies

Risk Factor	Risk Estimate	Risk Estimate in Combination With COCs	Recommendations for Prevention
Factor V Leiden heterozygote	4–8 times[16,86]	28–35 times[16]	Minimize acquired risks
Prothrombin G20210A heterozygote	2–3 times[36]	16 times[87]	Minimize acquired risks
Travel	2–4 times[55,88]	14–20 times[52,89]	Maintain hydration; frequent exercise of leg muscles; graduated compression stockings and/or pharmacologic prophylaxis if significant risk factors
Trauma/surgery	2–5 times[90–92]	5–12.5 times[93]	Consider discontinuation of COCs for 4–6 wk before surgery or after traumatic injury, considering the risks of pregnancy; consider adjusted thromboprophylaxis if within first year of COC use
Obesity	1.7–2.4 times[60]	10–24 times[60,94]	Weight loss
Smoking	1.4–3.3 times[61,95,96]	8.8 times[61]	Smoking cessation or decreased use

TABLE 4 Comparison of Recommendations for Use of Combined Hormonal Contraceptives

Clinical Situation	WHO[64, a]	UKMEC[65, a]	CDC[68, a]
History of VTE	4	4	4 if higher risk of recurrence of estrogen-associated VTEs, known thrombophilia, active cancer, recurrent VTEs; 3 if lower risk of recurrence, no risk factors
History of VTE, currently on anticoagulation therapy (for at least 3 mo)	4	4	4 if higher risk of recurrence (known thrombophilia, active cancer, history of recurrent VTEs)[b]; 3 if lower risk of recurrence, no risk factors[b]
Acute VTE	4	4	4
First-degree family history of VTE	2	2 (3 if family member was <45 y old)	2
Major surgery with prolonged immobilization	4	4 (suggest COCs be discontinued at least 4 wk before surgery)	4
Major surgery without prolonged immobilization	2	2	2
Known thrombogenic mutations (eg, factor V Leiden, prothrombin mutation, and protein S, protein C, and antithrombin deficiencies)	4	4	4
Obesity	2	2 (BMI < 35); 3 (BMI 35–39); 4 (BMI ≥ 40)	2
Postpartum (nonbreastfeeding) <21 d	3	3	3
Systemic lupus erythematosus with antiphospholipid antibodies	4	4	4

WHO indicates World Health Organization; UKMEC, United Kingdom Medical Eligibility Criteria; CDC, Centers for Disease Control and Prevention.

[a] Grading scale: 1 indicates no restriction (use method in all circumstances); 2, the advantages generally outweigh the risks (generally use method); 3, the risks usually outweigh the advantages (use not usually recommended unless no alternatives are available); and 4, the condition represents an unacceptable health risk if the contraceptive method is used (method not to be used).

[b] Clarification: women on anticoagulant therapy are at risk for gynecologic complications of therapy, such as hemorrhagic ovarian cysts and severe menorrhagia. Hormonal contraceptive methods can be of benefit in preventing or treating these complications. When a contraceptive method is used as a therapy, rather than solely to prevent pregnancy, the risk/benefit ratio may differ and should be considered on a case-by-case basis.

American College of Obstetricians and Gynecologists has published recommendations for various noncontraceptive uses of hormonal contraceptives and for use of hormonal contraception in women with coexisting medical conditions as practice bulletins.[66,67] In 2010, the Centers for Disease Control and Prevention released the *U.S. Medical Eligibility Criteria for Contraceptive Use*,[68] which complement the recommendations from the American College of Obstetricians and Gynecologists, allowing consideration of COCs for patients with VTEs attributable to a reversible trigger or for those who are currently receiving anticoagulation therapy. For example, previous VTE on COCs or with pregnancy is an absolute contraindication to COCs, whereas line-associated VTEs or others with low recurrence risk are reasonably considered relative contraindications to COCs. All of these groups recognize that, in general, most of the medical risks of hormonal contraceptives are heightened in older patient groups, and complications such as VTEs are much less common in adolescents.

Despite the attention paid to inherited thrombophilias, none of the guidelines recommend routine screening. The cost of screening and the number of patients needed to screen to prevent VTEs, especially life-threatening VTEs, are both very high. In addition, screening may produce false reassurance, increased anxiety, hypervigilant management, additional familial screening, and significant unnecessary expense.

These clinical guidelines are reviewed here to promote awareness and to offer a framework for approaching management decisions for individual patients. Clinical decisions may ultimately differ from these established guidelines as a result of patient preferences, lack of treatment availability, other health issues or because the guidelines simply do not explicitly address a particular clinical scenario. Although published guidelines consider thrombophilia an absolute contraindication to COCs (level 4), we and others have addressed challenging presentations of young women with identified thrombophilia without thrombosis through balanced discussions about absolute and relative risks of VTEs.[69] When considering VTE risk, our group gives greater weight to a personal history of thrombosis than thrombophilia ascertained by screening. Fortunately, the availability of new methods of hormone replacement and of contraception has provided clinicians with more options than were available previously to address medical problems. For example, this question may arise: "Does anticoagulation offset the thrombotic risk associated with COCs?" The Centers for Disease Control and Prevention guidelines indicate that COCs in this setting would pose an unacceptable health risk to those with higher risk for recurrent VTEs (level 4) and that the risks would usually outweigh the benefits for those at lower risk for recurrent VTEs (level 3). However, both

statements are accompanied by a brief clarification (see Table 4). Particularly challenging situations include anticoagulation for a VTE attributed to previous COC use and menorrhagia while on anticoagulation therapy. Women with a personal history of unprovoked thrombosis or ongoing thrombophilia (inherited or acquired) can safely receive prophylactic anticoagulation through pregnancy and the postpartum period with successful reduction in VTE risk.[70] Because COCs carry less thrombotic risk than pregnancy, it is logical that COCs would be generally safe in many women on anticoagulation therapy. For those with menorrhagia who are on anticoagulant medications, the intensity of anticoagulation would need to be reevaluated and products with lower thrombotic risk such as continuous or cyclic progestin therapy (norethindrone) used as first-line therapy. The levonorgestrel intrauterine system also seems to be both effective and well tolerated for menorrhagia with concurrent anticoagulation therapy.[71] In some cases, depot leuprolide and progestin add-back or even COCs may ultimately be needed to control menorrhagia or hemorrhagic ovarian cysts. Thus, the decision should remain individualized, and the specific indication for anticoagulation should be considered.

USES OF HORMONES IN ADOLESCENTS

In addition to evaluating a patient's risk of thrombosis with the use of COCs, it is important to weigh carefully the therapeutic benefits of COCs for each individual patient on the basis of her specific clinical indication (Table 5), the likelihood of adherence, the efficacy of alternative treatments, and the potential noncontraceptive benefits. Taking the example of contraception, if an adolescent wants to use COCs, the preferable progestins would be those with the lowest risk of VTEs (norgestrel, levonorgestrel, norethindrone, or norgestimate); some patients will prefer other formulations, and more studies are needed to assess the risk of drospirenone-containing COCs, particularly for the first year of use. Pregnancy itself is associated with a greater risk of VTEs than all the COCs.[72] Although progestin-only options might seem preferable for some, they are associated with more irregular menses, a narrower window of time for taking the pill, and fewer benefits for girls with acne, hirsutism, or polycystic ovarian syndrome than COCs. Long-acting progestin-only methods such as depot medroxyprogesterone acetate, etonogestrel implants (eg, Implanon [Schering Corporation, Kenilworth, NJ]), or the levonorgestrel intrauterine system[73] offer higher efficacy than progestin-only pills, but the irregular menses and lack of improvement of hyperandrogenism still favor COCs for many adolescents. However, in the presence of a higher thrombotic risk, progestin-only pills or nonhormonal methods are indicated for many of the conditions listed in Table 5, such as dysmenorrhea that does not respond to nonsteroidal anti-inflammatory drugs. A similar rationale can be applied to each potential indication for COCs. It is important to note that the patient should always be counseled to improve modifiable risk factors.

Treatment of mild DUB includes cyclic progestins and iron replacement, whereas treatment of moderate-to-severe DUB typically includes COCs (1–4 times per day initially). For those with se-

TABLE 5 Our Approach to Treatment Options and Hormone Therapies Amidst Thrombotic Risk

Problem	First-Line Treatment	With Minor Thrombophilia (Obesity, Travel, Smoking)	With Major Thrombophilia (Surgery With Immobilization, Inherited Thrombophilia)	History of Thrombosis
Contraception	COC, DMPA, LNG-IUS, ETG	COC, POP, DMPA, LNG-IUS, ETG	POP, DMPA, LNG-IUS, ETG	POP, LNG-IUS, DMPA, ETG
Dysmenorrhea	NSAID, COC	NSAID, COC	POP, DMPA	POP, DMPA
DUB, mild or moderate	Cyclic progestin (MPA, NET), COC	Cyclic progestin (MPA, NET), COC	Cyclic or continuous progestin (NET)	Cyclic or continuous progestin (NET)
DUB, severe	COC	COC	NET, GnRH-a with NET add-back; LNG-IUS	NET, GnRH-a with NET add-back, LNG-IUS
Hypothalamic amenorrhea	Weight gain, nutrition, COC, transdermal E2 and progestin (NET, MPA)	COC, transdermal E2 and progestin (NET, MPA)	Transdermal E2 and progestin (NET, MPA)	Transdermal E2 and progestin (NET, MPA)
Polycystic ovary syndrome (PCOS)	COC, lifestyle change, metformin	COC, POP, cyclic progestins, metformin	POP, cyclic progestins, metformin	POP, cyclic progestins, metformin
Endometriosis	Continuous COC, NET, POP, DMPA, GnRH-a and add-back (estrogen/progestin or NET)	continuous COC, NET, POP, DMPA, GnRH-a and add-back (estrogen/progestin or NET)	GnRH-a and NET add-back, NET alone, DMPA	GnRH-a and NET add-back, NET alone, DMPA
Primary ovarian insufficiency (POI)	Transdermal E2 and cyclic progestin (NET, MPA), COC	Transdermal E2 and cyclic progestin (NET, MPA), COC	Transdermal E2 and cyclic progestin (NET, MPA)	Transdermal E2 and cyclic progestin (NET, MPA)

DMPA indicates depot medroxyprogesterone acetate; LNG-IUS, levonorgestrel intrauterine system; ETG, etonogestrel implant; POP, progestin only pills, norethindrone 0.35 mg/day; NSAID, nonsteroidal anti-inflammatory drug; MPA, oral medroxyprogesterone; NET indicates norethindrone 5 to 15 mg/day; GnRH-a, gonadotropin-releasing hormone agonist; E2, 17-β estradiol. In this table, COC includes the transdermal patch and vaginal ring.

vere DUB and anemia along with higher risk of thrombosis, a progestin-only regimen such as norethindrone (5–10 mg, given 1 to 4 times per day) should be initiated. Note that these high doses of norethindrone acetate (20–40 mg/day) have been reported to result in measurable serum ethinyl estrogen levels[74]; the potential thrombotic risk is unclear to date. The levonorgestrel intrauterine system offers another promising option for adolescents with heavy menses who are candidates for insertion and have balanced the risks and benefits of use. Gonadotropin-releasing hormone agonists may be necessary for longer-term control and can also be used prophylactically for girls undergoing bone marrow transplants to prevent menorrhagia. Desmopressin (Stimate [CSL Behring, King of Prussia, PA]) may be needed in the setting of von Willebrand disease, and aminocaproic acid or tranexamic acid (antifibrinolytics) are used in rare circumstances.[75]

For endometriosis, although COCs reduce pain and disease progression,[76] progestin-only therapies (oral norethindrone, depot medroxyprogesterone acetate) or gonadotropin-releasing hormone agonists with progestin-only add-back should be used in the setting of increased thrombotic risk.[77–79]

Estrogen replacement in the appropriate settings offers a variety of benefits including support of bone mineral accrual.[80] Although patients with anorexia nervosa are treated best with weight restoration,[81–83] normal-weighted girls with hypothalamic amenorrhea may benefit from HRT. The American College of Sports Medicine has recommended estrogen/progestin therapy to girls older than 16 years with normal weight and nutritional intake who have loss of bone density caused by low estrogen levels; they noted that their recommendation was based on case studies, consensus opinion, and usual practice (level C-2 evidence).[84] Although varying doses and types of estrogen/progestin have been prescribed, transdermal estradiol offers the significant advantage of a physiologic replacement estrogen without evidence of increased risk for VTEs. However, COCs may be prescribed for convenience or for contraception in these girls.

There are many other indications for COCs including premenstrual dysphoric disorder, acne, prevention of menstrual migraines, and prevention of ovarian cysts. A similar approach can be applied for these indications. However, in general, in the setting of high thrombotic risk, COCs should not be used, and alternative therapies should be used.

PRACTICAL APPLICATION

When faced with choices regarding hormone therapies in the setting of thrombotic risk, we suggest awareness of the available guidelines and thoughtful evaluation of whether they apply to the particular patient or not. We have found that these discussions can help patients and families assess the risks and benefits of therapeutic decisions. Clinical judgment, knowledge of guidelines, and individualized management are essential steps in presenting options. The following is an approach that we have found helpful.

1. Evaluate the indication for hormone therapy, whether both estrogen and progestin are needed, and the quality of alternatives (eg, nonhormonal contraception).
2. Assess and counsel the patient regarding her thrombotic risk factors, inherited and acquired, and give maximal weight to a personal history of thrombosis.
3. Assess the patient's pregnancy risk factors, offer education regarding the risks associated with unplanned pregnancy, and discuss pregnancy-prevention measures.
4. Whenever possible, assess the absolute risk of thrombosis for each individual patient to assist in the interpretation of relative-risk data.
5. Discuss the therapeutic options with the patient, considering what is known about the relative risks of the various dosages, hormone types, and modes of administration.
6. Assess the patient's preferences.
7. Educate the patient regarding thrombosis-prevention measures, modifiable risk reduction, and symptoms of VTEs.

If hormone therapies are being considered for contraceptive purposes, the significant risks from unplanned pregnancy should be fully incorporated into decision-making and compared with the overall low absolute risk of thrombosis associated with hormone therapies.

With the increasing attention paid to these risks not only in medical meetings, the media, and courts but most importantly among patients and their families, we have found it useful to have multidisciplinary discussions and to balance risks and benefits for individual complex patients. The ability to estimate and articulate the absolute and relative risks for thrombosis and summarize the evidence regarding specific hormone therapies can aid pediatricians in delivering optimal health care to adolescents and young women.

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