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REVIEW

Hormonal therapies in females with blood disorders: thrombophilia, thrombosis, hemoglobinopathies, and anemias

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Abstract

There is widespread use of gonadal steroid hormone therapy for a variety of indications throughout the reproductive and postreproductive lifespan. These therapies may have particular benefits and specific risk among those with blood disorders, including inherited or acquired bleeding disorders, thrombophilia, thrombosis, or anemia. This clinical review is intended to provide a guidance for counseling and management of adolescent and adult biologic females with thrombophilic risk factors and/or thrombosis who require hormonal therapy. In general, synthetic estrogens present in contraceptive products should be avoided in those with a personal or strong family history of thrombosis or thrombophilias. In contrast, natural estrogens present in formulations for climacteric symptom management do not need to be avoided, and vaginal or transdermal formulations are preferred. Likewise, transdermal estradiol is preferred for gender-affirming hormone therapy and requires individualized assessment in those at high risk of thrombosis. Progestogens (either synthetic progestins or naturally occurring progesterone) can be used safely in nearly all patients. There is minimal safety evidence among anticoagulated patients at risk for thrombosis, which requires a patient-specific approach when discussing hormone therapies.

KEYWORDS
anemia, estrogen, progestin, thrombophilia, thrombosis

Essentials

- Dosing and formulations of hormonal therapies vary based on intended use.
- Estimates of thrombosis risk are based on contraceptive and menopausal dosing.
- We review thrombosis risk with gender-affirming hormone therapy and menstrual management.
- We summarize hormonal therapy for people with blood disorders.

BOX 1. Indications for hormone therapies

Acne or hyperandrogenism
Bone mineral density
Bleeding due to fibroids
Contraception
Dysmenorrhea
Endometriosis
Gender-affirming therapy
Genitourinary syndrome of menopause
Heavy menstrual bleeding
Menstrual suppression
Menstrual regulation
Pelvic pain
Polycystic ovarian syndrome
Premenstrual dysphoric disorder
Premenstrual syndrome
Prevention of ovarian cysts
Primary ovarian failure
Vasomotor symptoms
Vulvovaginal atrophy

1 | INTRODUCTION

Estrogen and/or progestogen-containing hormonal therapies are indicated in women, girls, and biologic females for several reasons (Box 1). When selecting the most appropriate therapy, people with the potential to menstruate with blood disorders require careful consideration. In particular, these individuals may derive great benefit from hormonal methods to manage menstrual bleeding, while risk of specific methods may outweigh benefits in those with a history of thrombosis or thrombophilias. This clinical review summarizes benefits, risks, and considerations for use of a wide variety of hormonal therapy formulations among individuals with blood disorders, including inherited and acquired thrombophilia, thrombosis, hemoglobinopathies, and anemia. This guidance follows a previously published thorough review of estimated risk of venous thrombosis in healthy users of specific gonadal steroid hormone products [1].

1.1 | Benefits of hormone therapy

Benefits of gonadal steroid hormone therapy among people with blood disorders include menstrual management, contraception, climacteric symptom management, gender-affirming care, and symptom management related to ovulation disorders. However, people with blood disorders are usually excluded from clinical trials for these indications. Heavy menstrual bleeding (HMB) is common, affecting up to 30% of menstruating adults [2,3]. These individuals are at increased risks of developing iron deficiency anemia, experiencing obstetric or postprocedural bleeding, enduring chronic pain, and experiencing decreased quality of life [4,5]. Individuals at risk for thrombosis are among the many who experience HMB. Moreover, people with the potential to menstruate who develop thrombosis and require anticoagulation may have significant worsening of their HMB [6]. These individuals are underrepresented in randomized trials and registries for the acute treatment of venous thromboembolism (VTE) [7]. Further investigation is needed to understand the benefits and challenges of the use of hormonal therapies for a variety of indications in people with blood disorders.

1.2 | Risk vs benefit

Much of the information included in this manuscript has been adapted and modified from the 2016 United States Medical Eligibility Criteria (MEC) for contraceptive use, which addresses the safety of the use of contraceptives in those with certain characteristics or underlying medical conditions [8]. This tool is available as a document, table, and mobile app. These recommendations are for the safety of use of specific contraceptive methods for pregnancy prevention in the setting of thrombophilic risk factors, among other medical conditions. When a contraceptive method is used as a therapy to treat a medical condition, such as vasomotor symptoms during perimenopause or abnormal menstrual bleeding, rather than solely to prevent pregnancy, the risk/benefit ratio may be different and should be individualized using these recommendations as a guideline.

Risk/benefit profiles may change with aging, particularly during perimenopause. While no methods are contraindicated based on age, initiation and continuation of estrogen-containing methods should include a basic cardiovascular evaluation, including periodic blood pressure evaluation and assessment for the onset of new medical conditions [9,10]. In particular, gallbladder disease, hypertension, migraine headache with aura, personal history of breast cancer, smoking, or multiple cardiovascular risk factors should prompt a re-evaluation.

1.3 | Pregnancy prevention and preparation

People with the potential to menstruate with blood disorders may have conditions that require preconception planning or medication adjustments, including due to teratogenic effects, so use of highly effective contraception is often recommended for those exposed to the possibility of pregnancy. If desired, contraception is recommended through menopause, defined as 2 years of amenorrhea prior to the age of 50 years and 1 year of amenorrhea after the age of 50 years [11]. All hormonal therapies approved for contraceptive use are highly effective, although the relative effectiveness of methods may vary due to user adherence, dual use with other family planning practices, and by age, due to age-based fertility [12].

2 | THROMBOSIS RISK BASED ON HORMONE TYPE

Gonadal steroid hormones can be associated with an increased risk of thrombosis, and this risk will vary depending on the type of hormone therapy and dosage, as well as patient-related factors.

TABLE Hormone therapy options.

Contraceptives	
Progestogen therapies	**Duration/frequency**
Subdermal etonogestrel implant	3 y
Levonorgestrel intrauterine device[a]	3-6 y
Depot medroxyprogesterone acetate injection	3 mo
Oral norethindrone 0.35-mg tablet	Daily continuous only
Oral drospirenone 4-mg tablet	Daily cyclic (24/4) or continuous
Combined therapies	**Duration/frequency**
Oral EE/P (20-35 mcg EE) tablet	Daily cyclic (24/4, 21/7) or continuous
Oral E2V/dienogest[a] tablet	Daily cyclic only
Oral E4/drospirenone tablet	Daily cyclic (24/2) or continuous
Transdermal EE/P patch	Changed weekly, cyclic (3/1)
Intravaginal EE/P ring	Changed monthly or annual, cyclic or continuous
Menstrual therapy	
Progestogen therapies	**Duration/frequency**
Oral norethindrone acetate 5-mg daily to 3 times a day tablet	Daily cyclic (24/4) or continuous
Oral medroxyprogesterone acetate (5-20 mg) tablet	Daily continuous or cyclic
Peri-/menopausal hormone therapy	
Estrogen therapies	**Duration/frequency**
Transdermal estradiol patch (with progestin if uterus present)	Changed semiweekly
Topical estradiol gel (with progestin if uterus is present)	Daily
Oral estradiol tablet (with progestin if uterus is present)	Daily
Vaginal estradiol tablet	Semiweekly
Vaginal estradiol ring	Changed every 3 mo
Vaginal estradiol cream	Semiweekly
Combined therapies	**Duration/frequency**
Oral estradiol (1 mg)/norgestimate tablet	Daily cyclic
Oral EE (10 mcg)/NETA tablet	Daily cyclic
Transdermal estradiol/NETA patch	Semiweekly

E2V, estradiol valerate; E4, estretol; EE, ethinyl estradiol; NETA, norethindrone acetate; P, progestin.
[a]Contraceptives with dual indication for heavy menstrual bleeding.

2.1 | Types of hormone therapies

Gonadal steroid hormone therapies can be classified into 2 categories: progestogen-only or combined, containing a form of estrogen and progestogen (either synthetic progestins or naturally occurring progesterones; Table). Most formulations are developed for use as contraceptives, some are developed for management of menstrual irregularities, and some are intended for peri- or postmenopausal symptom management. The estrogen components vary greatly in terms of potency and bioavailability, with ethinyl estradiol (EE), estradiol valerate (E2V), and estetrol (E4) used in contraceptives and estradiol (E2) and conjugated equine estrogens (primarily estrone) used in menopausal symptom management and gender affirmation therapy. The bioavailability and pharmacokinetics of each of these medications vary based on the method of delivery (ie, transdermal, subdermal, oral, and transvaginal). The potency of estrogens depends on the formulation (ie, synthetic and conjugated) [13]. The progestogens have varying dose-dependent effects on the endometrium and the ovary and may modulate the effect of estrogens [14].

2.2 | Estrogen procoagulant effects

All estrogens activate hepatic pathways that increase the production of procoagulant proteins such as factor VII, factor VIII, factor X, von

Willebrand factor, and fibrinogen. The relative impact depends on the type of estrogen, dose, and route of administration [15–17]. Oral administration results in the highest liver exposure due to its first-pass effect. The synthetic estrogen EE is considerably more potent (approximately 100×) than natural E2 and results in clinically important hepatic activation with oral or parenteral administration. When given orally, estradiol induces procoagulant proteins, but this effect is minimal when administered parenterally in physiologic doses. Following oral administration of E2V, gastrointestinal metabolism results in a hepatic impact equivalent to estradiol. Another recently introduced estrogen in oral contraception is the naturally occurring estretol (E4), which is a very weak estrogen with minimal liver impact when taken orally. Whether these effects influence thrombosis risk awaits clinical evidence from phase 4 studies.

2.3 | Progestin procoagulant effects

There are no direct procoagulant effects of progestins via the hepatic pathway. Progestins via oral, intrauterine, and subdermal implant routes are not associated with increased procoagulant activity or thrombotic risk, even at higher risk times such as postpartum [18–22]. However, in combination products, progestins modulate the procoagulant effect of estrogen to varying degrees [23–25]. Additionally, a dose-dependent small proportion (<0.3%) of norethindrone (NET) and norethindrone acetate (NETA) aromatizes to EE, equivalent to 20 mcg of EE for 10 mg of NETA [26]. NETA, typically administered at 5 mg daily up to 3 times daily for menstrual management or ovulation suppression, is rapidly hydrolyzed to NET and thereafter has similar pharmacodynamics as NET, which is typically administered at 0.35 mg daily as a contraceptive product. Injectable depot medroxyprogesterone acetate (DMPA) is also associated with a small increased risk in thrombotic events through an unknown mechanism [27]. Although this finding may be the result of higher-risk patients choosing this method, clinical guidance uses a separate category for DMPA, which recommends avoiding its use in those at higher risk of VTE. Thus, anticoagulation is recommended in those initiating or continuing use of DMPA with a history of prior VTE. Further evaluation of progestin dosing and pharmacodynamics, particularly for NETA and oral MPA, is needed to determine a threshold level that is considered safest in higher-risk patients.

3 | THROMBOSIS RISK BASED ON HORMONE THERAPY INDICATION

3.1 | Hormone therapy in peri- and postmenopausal females

Hormone therapy (HT) typically contains E2 instead of EE, which is associated with decreased thrombogenicity. HT is available in oral, transdermal, and intravaginal forms. Transdermal and intravaginal forms of estradiol are associated with a lower risk of VTE compared to oral formulations, although a decision about individual use may be based on underlying cardiovascular health [28–30]. Mobile app decision aids can be helpful for this evaluation, are based on assessment of underlying cardiovascular risk, and take into account the time since menopause, symptom profile, and cancer [31,32]. HT is available in estrogen-only or combined estrogen/progestin combination formulations. The estrogen-only approach requires endometrial protection with combination progestogen therapy in individuals with an intact uterus because unopposed estrogen dramatically increases the risk of endometrial cancer [33]. In those at increased risk of thrombosis who require estrogen for symptom management, transdermal or intravaginal routes are preferred. A meta-analysis of 15 observational studies showed oral estrogen therapy to be associated with increased risk of a first episode of VTE in postmenopausal women when compared to transdermal estrogen (RR, 1.63; 95% CI, 1.40-1.90) [34].

3.2 | Gender-affirming hormonal therapies

Gender-affirming therapy for transgender females may include use of estrogen, typically estradiol. The most common modes of delivery are oral, intramuscular, or transdermal. There is some evidence that estrogen therapy is associated with increased risk of VTE and ischemic stroke among transgender females beyond that of cisgender males and females [35–37]. Risk of thromboembolic events should be discussed before initiating estrogen as a gender-affirming therapy. Users should be encouraged to avoid smoking and maintain a healthy weight, cholesterol, and blood pressure [37]. Users should also discuss with their healthcare providers the risks and benefits if they have personal or family history of VTE or known thrombophilia. Research does not currently support routine thrombophilia screening or use of aspirin/anticoagulation prophylaxis in transgender females at high risk for thrombosis [38]. If these patients develop thrombosis, available evidence favors continuing estrogen therapy as long as the patients are on appropriate anticoagulation. Limited data suggest that transdermal estrogen may carry lower thrombosis risk in this scenario. Further research is necessary to clarify the degree of risk based on formulation, mode of delivery, and more accurate risk assessment [37].

Gender-affirming therapy in transgender males may include use of androgen therapies, including testosterone. There is no conclusive evidence that transgender males using testosterone have an increased risk of thromboembolic events [35]. Transgender males may use combined or progestin-only hormonal therapies for contraception, menstrual management, or for other indications, and there are no clear recommendations for concomitant use of these medications with testosterone [39].

3.3 | Contraception and menstrual management

Contraceptive products are frequently used for menstrual management indications, and there are also products (such as NETA or MPA)

BOX 2. Patient- or disease-related VTE risk factors

Acquired thrombophilia (antiphospholipid syndrome)
Age
Burns
Cancer
Central venous catheters
Estrogen
Family history of VTE or inherited thrombophilia
Hospitalization
Immobility
Infection
Inflammatory bowel disease
Long distance travel
Medications such as steroids and chemotherapy (asparaginase)
Nephrotic syndrome and other protein losing conditions
Obesity
Personal history of VTE
Pregnancy/postpartum
Smoking
Surgery
Systemic lupus erythematosus
Trauma

VTE, venous thromboembolism

that are contraceptive based on the dose, but have indications only for abnormal uterine bleeding. The overall VTE risk of estrogen-containing contraceptive products is approximately 2-fold higher than baseline risk. The clinical impact of the progestin component in combined methods is minimal after taking into account baseline patient-related risk factors for VTE, such as age, weight, and inherited or acquired thrombophilias (see Box 2) [40].

3.3.1 | Combined hormonal therapies

Combined hormonal therapy refers to those products including an estrogen and a progestin, which may be delivered in the same product (transdermal, transvaginal, oral, and intramuscular) or may be 2 products used concomitantly (eg, oral and subdermal implant or intrauterine). Combined therapies are common in contraceptive products. All formulations containing synthetic estrogens (EE or E2V) are associated with an increased risk of venous thromboembolism (VTE) [15–17]. In addition to patient-related factors, the degree of risk also depends on the generation and dose of estrogen and type of progestin. The relative risk (RR) of VTE with combined oral contraceptive use has been reported to be 2- to 6-fold higher than the baseline risk in the general population. The absolute risk for VTE in nonusers of contraceptives includes a background risk of 0.19 to 0.37 per 1000 woman years [15]. The use of combined oral contraceptives increases the risk 4-fold (RR, 3.5; 95% CI, 2.9-4.3), as shown by a network meta-analysis [15]. This is a dose-dependent effect, with combined oral therapies containing 50 mcg of EE having the highest risk for VTE [15].

The route of administration of combined hormone therapies may impact thrombotic risk, but it is unclear. A systematic review comparing users of oral combined HT to transvaginal ring users documented conflicting results (1 study showing increased risk among ring users, whereas 2 others did not find statistically significant differences) [27].

The type of progestogen used in combination methods may impact thrombotic risk. Third- and fourth-generation progestogens such as desogestrel, gestodene, drospirenone, and cyproterone acetate were associated with a higher risk of VTE (RR ranging from 1.27 to 2.04) in various published studies, when used in combination with EE, than second-generation progestogens [15,17,41]. One possible explanation for this is higher-risk users of these products [40].

3.3.2 | Progestin therapies

In general, progestin-only therapies present in contraceptive products (oral, intrauterine, and subdermal implant) carry a significantly lower risk for thrombosis when compared to estrogen-containing formulations [27]. Oral norethindrone and levonorgestrel are not associated with an increased risk of thrombosis [27,42]. Many clinicians have concerns about the use of oral drospirenone (DRSP) in patients with thrombosis risk due to higher RR of thrombosis in users of DRSP combination products with EE compared to combination products with second-generation progestins [1,15]. However, there is no evidence of changes in hemostatic parameters in users of DRSP without EE [19]. Subgroup analysis suggested a higher risk of thrombotic events for those using an injectable progestin (3 studies reported increased OR ranging from 2.2 to 3.0 for DMPA), but not for those using oral progestins or an intrauterine progestin [40]. Despite product insert warnings, there is no evidence of elevated risk of VTE with the etonogestrel implant, which has recently been resubstantiated in a large nested matched case-control study (adjusted odds ratio, 1.09; 95% CI, 0.74-1.61) [42]. The Food and Drug Administration label contraindication for use of the etonogestrel subdermal implant Nexplanon in those with history of VTE is based on studies on VTE risk with the etonogestrel precursor desogestrel administered orally in combination with EE [43]. Given the label, it is prudent to discuss a balance of individual risk and benefit particularly in those with prior personal or family VTE history or other significant risk factors for VTE such as obesity.

The same large study did demonstrate potential clinical concern about the relationship between recent users of 2.5 to 10 mg of NETA and VTE, which occurred in 41% users vs 11% controls (adjusted odds ratio, 3.00; 95% CI, 2.17-4.15) [42]. Notably, this was not a dose-dependent effect after adjusting for VTE risk factors. Elevated VTE risk was not observed with contraceptive NET doses at 0.35 mg/d or even with NET doses of ≥0.7 mg/d. The lowest effective dose of NET/NETA for menstrual suppression may be as low as <2.5 mg, which should remain an option among higher-risk patients.

4 | CLINICAL RECOMMENDATIONS IN VENOUS THROMBOSIS, THROMBOPHILIA, AND MEDICAL CONDITIONS PREDISPOSING TO THROMBOSIS

4.1 | Venous thrombosis

4.1.1 | Acute deep vein thrombosis/pulmonary embolism

Immediately following acute thrombosis, many patients discontinue all hormonal therapies, leaving them without contraception or menstrual management, even in the setting of ongoing anticoagulation. However, avoidance of pregnancy through use of highly effective contraception is strongly encouraged during the first 3 months after an acute VTE due to the increased risk of recurrence [44]. Those at risk for pregnancy should be provided information about effectiveness and education about safety of all options, including hormonal therapies.

Among those who are menstruating, the likelihood of increased menstrual blood loss with use of anticoagulation should also be taken into consideration. Initiation of combined hormonal therapies in this acute setting is typically discouraged due to the thrombogenic risk, although data suggest that this risk is mitigated by the use of therapeutic anticoagulation [45]. Therefore, immediate discontinuation of combined hormone therapies, particularly among those with HMB, may do more harm than good. There is no direct evidence for risk of recurrent VTE being related to progestin-only therapies, and continuation or initiation of progestin therapies is the standard following acute thrombosis. Although considered category 2 by the US MEC after acute VTE, the slight association of injectable DMPA with risk of VTE in population studies should be considered a relative contraindication to initiating this method [40].

4.1.2 | Deep vein thrombosis/pulmonary embolism and established anticoagulant therapy for at least 3 months

While the risk of recurrent thrombosis is expected to decline over time in patients with a provoked VTE, this patient population remains at increased risk of thrombosis with pregnancy [46]. In addition, there are potential teratogenic effects with some anticoagulants. Therefore, avoiding unplanned pregnancy during and after anticoagulant therapy is strongly encouraged. The levonorgestrel-containing intrauterine device (LNG-IUD), in particular, is both highly effective for preventing pregnancy and a useful treatment for HMB, which is present in up to 70% of oral anticoagulant users [1].

Patients who need to continue anticoagulation past the initial 3-month period and who may desire pregnancy should be offered preconception counseling with an obstetrician and a hematologist whenever possible. The need to convert from an oral to parenteral agent, preferentially low molecular weight heparin, either prior to conception or at the first positive pregnancy test, should be emphasized [47].

4.1.3 | Remote history of provoked deep vein thrombosis/pulmonary embolism no longer on anticoagulation

Patients who are able to discontinue anticoagulant therapy should be advised about the importance of avoiding combined hormonal contraceptives, including the pill, ring, or patch in the future, as well as the importance of avoiding oral estradiol. Progestin-containing contraceptive therapies, including the LNG-IUS and the subdermal implant, are effective contraceptive options.

Patients discontinuing anticoagulation therapy should be educated about whether prophylactic anticoagulation would be recommended in the antepartum and postpartum settings (such as patients with a history of estrogen-provoked events) or in the postpartum setting only (such as patients with surgically provoked VTE). Such patients will also benefit from preconception counseling when planning pregnancy.

4.2 | Inherited thrombophilias

Patients with inherited thrombophilias, including factor V Leiden, prothrombin gene polymorphisms (F5 rs6065 and F2 rs1799963), proteins C and S, and antithrombin deficiencies, are at increased risk of VTE events during pregnancy, surgery, and periods of immobility. [48,49] Those with a history of thrombosis in a first-degree family member are also at an increased risk, sometimes even in the absence of a detectable "thrombophilia" [48,49]. Conversely, others may have incidental findings of hereditary thrombophilias in the absence of personal or family history, such as from commercial genetic testing or inappropriately ordered tests [50]. Routine screening for inherited thrombophilias is not appropriate because of the rarity of these conditions and the high cost of screening. Management of hormonal therapy in the setting of an incidental finding or uncertain family history of thrombophilia should be individualized, and take into account the indication for treatment, concurrent risk factors for thrombosis, and alternative options for therapy. In most cases, synthetic estrogen should be avoided without the need for confirmatory testing.

Discussion of reproductive goals along with contraceptive provision and preconception planning should be integrated into routine care for those with inherited thrombophilia. If desired, relative safety of contraceptive options should be discussed. Progestin-only methods are preferred over combined methods for those with inherited thrombophilias due to thrombotic risk with estrogen-containing methods [8]. Progestin-only methods are generally preferred for patients with a family history of VTE in a first-degree relative regardless of documented thrombophilia. In such settings, testing for thrombophilia is unlikely to add significantly to management.

4.3 | Superficial venous disorders

Superficial venous thrombosis might be associated with an increased risk of VTE related to estrogens [51]. If risk factors for concurrent

deep vein thrombosis (DVT; eg, known thrombophilia or cancer) are present or there is an acute or prior DVT, refer to the recommendations for DVT/pulmonary embolism. Superficial venous thrombosis associated with a peripheral intravenous catheter is less likely to be associated with additional thrombosis, and the use of estrogen-containing methods may be considered.

4.4 | Arterial thrombosis

4.4.1 | Stroke (history of cerebrovascular accident)

Estrogen-containing therapies can promote not only venous but also arterial thrombosis, and should therefore avoided in those with a history of stroke. Stroke is rare among those of reproductive age, but may be associated with antiphospholipid antibody syndrome or other risk factors. Progestin therapies are preferred in those with a history of stroke. Among users of DMPA, there may be alterations in lipid metabolism, including reduced high-density lipoprotein levels, such that this method might be avoided in those with other cardiovascular risk factors [52–54]. However, little concern exists about these effects with regard to other progestins [55]. There is no evidence for or against the use of combined hormone therapies in those who are therapeutically anticoagulated and have a history of arterial thrombosis. As with history of VTE, discussion of reproductive goals along with contraceptive provision and preconception planning is essential due to risk of recurrence and potential teratogenic effects with some anticoagulants.

4.5 | Other medical conditions associated with increased thrombosis risk

4.5.1 | Migraine headache

Patients with a history of migraine headaches associated with aura are at increased risk of stroke in the setting of combined hormonal therapy use, and progestin-only methods are strongly preferred [56]. While this risk seems to be specific to migraines with aura, the Centers for Disease Control and Prevention MEC criteria state that for some patients, the risks may still outweigh the benefits [8].

4.5.2 | Autoimmune disorders including systemic lupus erythematosus and antiphospholipid antibody syndrome

Planning ahead and often avoiding pregnancy is very important for patients with autoimmune disorders and a) organ damage that precludes pregnancy, b) active disease that can negatively impact both maternal and fetal outcome, and c) on teratogenic medications. Combined hormonal contraception has been shown to be safe in randomized control trials in patients with inactive or stable active systemic lupus erythematosus and negative antiphospholipid antibodies (APAs) [57]. Estrogen therapy should be avoided in thrombotic and obstetric antiphospholipid antibody syndrome, nephrotic syndrome, active vasculitis, and APA, especially those with high-risk APA profile [57,58].

Patients with autoimmune disorders are at increased risk of both arterial thrombosis and VTE, and progestin-only methods are preferred. In severely thrombocytopenic patients with systemic lupus erythematosus, initiation of the copper IUD is not recommended due to bleeding risk, but continuation can be considered. The European League Against Rheumatism states that estrogens may be considered in fully anticoagulated patients carrying a low-risk APA profile for persistent gynecologic disorders not otherwise managed [57]. Progestin-only methods, including emergency contraception, will be safe alternatives for these patients. An individualized approach is utilized, considering disease status, patient preferences, prior history, reproductive goals, and RRs associated with pregnancy.

4.5.3 | Obesity

Patients with obesity not only have a 2 to 3-fold increased risk of VTE compared to nonobese patients [59,60], but certain methods of contraception may also be less effective in these patients based on limited studies categorizing effectiveness by body mass index (BMI) [61]. According to the CDC U.S. Medical Eligibility Criteria, combined hormonal contraceptives (oral, patch, and vaginal) are category 2 for a BMI of >35 kg/m^2 [8,62], as obese users may be at up to 10-fold increased risk of VTE vs obese nonusers [59,63].

5 | CLINICAL RECOMMENDATIONS IN THE SETTING OF CONGENITAL AND ACQUIRED ANEMIAS

5.1 | Congenital anemias

Anemia in menstruating individuals can be compounded by menstrual blood loss. Many contraceptive methods may be used to manage HMB or even induce amenorrhea to reduce these complications. Copper IUDs can increase blood loss, and patients with anemia should be counseled about this risk and offered alternative contraceptive methods.

5.1.1 | Thalassemia

Women and girls with worsening anemia/transfusion burden in the setting of menstruation who do not desire pregnancy may benefit from hormonal therapy to reduce menstrual blood loss. Patients with thalassemia, particularly those who have undergone splenectomy, may be at increased risk of thrombosis. However, the benefit of hormonal therapy is likely to outweigh the risk in the majority of patients. We recommend individual counseling taking all risk factors. Along with other heritable conditions, preconception evaluation and genetic counseling are recommended.

5.1.2 | Sickle cell disease

In addition to considerations regarding anemia and increase in pain crisis, sickle cell disease is associated with an increased risk of adverse health events during pregnancy. Therefore, discussion of reproductive goals along with contraceptive provision if desired and preconception planning should be integrated into routine clinical practice. Hormonal therapies may be considered. Data suggest that patients with sickle cell disease may be at increased risk of thrombosis and this concern needs to be discussed when considering hormonal therapy. There may be some benefit to use of DMPA in decreasing frequency of pain crisis [64–66]. At this time, it is reasonable to discuss risk and benefits of both progestin-only and combined estrogen-containing therapies in patients with sickle cell disease [64].

5.2 | Iron deficiency anemia

Iron deficiency anemia is a common complication of HMB. High-quality evidence supports the use of hormonal therapies and the LNG-IUD to reduce menstrual blood loss. Many individuals with HMB experience improved symptoms with any of the hormonal therapies, and therefore, all options should be discussed, in addition to iron supplementation and antifibrinolytic therapy [67].

6 | CONCLUSION

The increasing availability and use of gonadal steroid hormonal therapies for a variety of indications have dramatically improved the quality of life for women, girls, and people with the potential or prior potential to menstruate. Treatment of menstrual irregularities, the ability to prevent and plan for pregnancy, gender affirmation, and climacteric symptom management require a wide variety of pharmacologic formulations and delivery systems. Widespread use provides large-scale safety data across the lifespan for use in a variety of medical conditions. Medical benefits of hormonal therapies among those with blood disorders often exceed quality-of-life benefits, extending to treatment of life-threatening menstrual bleeding and avoiding and timing pregnancy. While avoiding potent synthetic estrogens dramatically reduces thombotic risks for those with and without underlying risk factors, benefits of estrogen may outweigh risks. Conversely, progestins and transdermal and vaginal estradiol, with progestin endometrial protection when needed, are safe in nearly all individuals.

7 | FUTURE DIRECTIONS FOR RESEARCH

Inclusion of people with the potential to menstruate who have blood disorders into clinical trials for a variety of patient-reported quality-of-life outcomes related to blood disorders would significantly impact the ability to provide evidence-based care. In particular, clinical trials of HMB therapeutics should include individuals with blood disorders.

Understudied areas are as follows:

- The safety of estrogen-containing products in individuals who are on anticoagulant therapy for a history of thrombosis.
- RR of thrombosis based on route of delivery of estrogen-containing products in gender-affirming therapy.
- Risk of thrombosis when using gender-affirming hormonal therapies in the setting of additional risk factors (surgery, medical comorbidities, tobacco use, etc.).
- RR of thrombosis with use of higher-dose progestogens (NETA, MPA) in the setting of thrombophilic risk factors.
- Safety, efficacy, and/or the need of anticoagulation dose adjustments in morbidly obese patients.

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M.K.B. contributed to writing substantial portions of the manuscript, and edited and revised the manuscript. B.S.B., R.P.R., N.S., and L.K.S. contributed to writing and editing and reviewed the final version. L.K.S. organized the writing team.

RELATIONSHIP DISCLOSURE

M.K.B. is a consultant for Bayer Pharmaceuticals and Exeltis Pharmaceuticals, and a medical and scientific advisory board member of the National Hemophilia Foundation. M.K.B. has received NIH grant funding as a Women's Reproductive Health Research K12 Scholar, has received consulting fees from Tremeau pharmaceuticals, serves on the medical advisory committee for the Foundation for Women and Girls with Blood Disorders, and has received honoraria for presentations for the Hemophilia Federation of America and the NHF, as well as for a book chapter on contraceptive technology. B.S.B. received grant funding from the FWGBD. R.P.R. is the president-elect of the Pulmonary Embolism Response Team Consortium; serves on the advisory board of the Pepper Trial; and receives consulting fees from Abbott, BMS, Dova, Janssen, Inari, and Penumbra. R.P.R. also receives research funds to her institution from BMS, Janssen, and is a consultant/advisory board member of Abbott, Bristol Meyer Squibb, Dova, Inari, Janssen, and Penumbra. N.S. has received honoraria from the HFA. L.V.S. reports no competing interests to disclose.

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