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REVIEW

Bleeding and Clotting Disorders in Pediatric and Adolescent Gynecology

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Abstract

Purpose of review This review aims to evaluate the diagnosis and management of adolescents with bleeding or clotting disorders, with a specific focus on how these effect contraception and heavy menstrual bleeding.

Recent findings In patients with bleeding disorders, tranaxamic acid may be a good addition to hormonal management options. In adolescents with a history of venous thromboembolism, it is important to continue a safe contraception method to prevent unintended pregnancy.

Summary A wide range of bleeding and clotting disorders affect adolescents, and there are multiple hormonal and nonhormonal options that can be used for treatment of heavy menstrual bleeding and contraception in these patients.

Keywords Bleeding disorders · Clotting disorders · Von Willebrand disease · Venous thromboembolism

Introduction

Heavy menstrual bleeding (HMB) is a common gynecologic problem in adolescents, affecting an estimated 12–37% of individuals, and is associated with substantial physical, psychosocial, and educational consequences. In this population, HMB most frequently results from anovulatory bleeding due to immaturity of the hypothalamic–pituitary–ovarian axis, however it may may also serve as an important indicator of an underlying bleeding disorder (BD). Conversely, venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolisms (PE), are rare but serious adverse events in children and adolescents. Timely recognition and appropriate management of HMB and VTE are essential optimize long-term outcomes of adolescent patients.

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The Menstrual Cyle in Adolescents

Following menarche, physiological maturation of the HPO axis occurs over several years, during which adolescents often experience menstrual cycles that do not yet match those of adults, which average 28 days (range 24–35 days). The majority of irregular cycles become ovulatory by two years post-menarche, with about 80% of cycles falling within the 21–45-day range [1, 2]. Among those who begin menstruating before age 12, approximately 50% of cycles are ovulatory by one year post-menarche, whereas only 50% of those who begin after age 13 will have regular cycles within 4.5 years of menarche [3]. Full reproductive maturity may take as long as eight years following menarche [4]. Clinical physicians' knowledge of menstrual patterns in adolescent girls, along with their ability to identify abnormalities, can enable early detection of potential health problems. As the menstrual cycle is considered an important vital sign of overall health, careful evaluation during adolescence is essential [5].

Heavy Menstrual Bleeding (HMB)

Although average menstrual blood loss is about 30 mL per cycle and volumes exceeding 80 mL are considered heavy, this definition has limited clinical usefulness because blood

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loss is not typically measured in such a fashion. Menstrual flow that requires changing hygiene products every 1–2 h, using double protection, causes frequent flooding through clothes or bedding, bleeding lasts longer than 7 days or involves passing clots is considered HMB. Ultimately, HMB is best defined as menstruation that is prolonged or excessive to the extent that it limits physical comfort, emotional health, participation in daily activities, or overall quality of life [6].

HMB Evaluation

HMB is a common gynecologic concern among adolescents, with a reported prevalence of 12–37%. HMB can significantly affect an adolescent's quality of life, leading to school absences and limiting participation in sports and social activities [7–9]. Prompt recognition, diagnosis, and treatment can help prevent iron deficiency, anemia, the need for blood transfusions, and hospitalization.

Evaulation of HMB should follow the PALM–COEIN classification system [10]. See Fig. 1. In adolescents, structural causes of HMB are uncommon; instead, anovulatory bleeding resulting from immaturity or dysfunction of the HPO axis is the most frequent cause and typically occurs within the first 2–3 years after menarche.

HMB at menarche and in adolescence may also serve as an important indicator of an underlying BD, the second most commonly reported cause of HMB in this age group. The prevalence of BDs in girls with HMB ranges from 21 to 48% across different studies, with higher rates observed among those who require hospitalization [11–13].

Screening for an Underlying BD

Adolescents who report HMB and meet any of the four criteria outlined in the recommended screening tool should undergo laboratory evaluation for a BD [6]. See Fig. 2. Use of validated bleeding assessment tools, such as the International Society on Thrombosis and Haemostasis Bleeding Assessment Tool (ISTH-BAT), is also recommended for predicting BDs in adolescents referred for HMB [14]. See Table 1.

The most common BDs identified in adolescent girls with HMB include von Willebrand disease (VWD), platelet function disorders (PFDs), thrombocytopenia, and clotting factor deficiencies. The considerable variability in the reported prevalence of BDs in adolescents with HMB likely reflects multiple contributing factors, including heterogeneous study populations, wide differences in menstrual symptom severity, physiological fluctuations in coagulation factors across the menstrual cycle, and difficulties obtaining a reliable and standardized coagulation measurement. When taking a medical history, it is important to identify risk factors for BDs and obtain a detailed family history of bleeding, including menstrual history, hysterectomies, and associated blood transfusions. A thorough physical examination should also be performed, including a careful inspection of the skin for bruising, hematomas, and petechiae.

The North American Association of Pediatric and Adolescent Gynecology (NASPAG) and American College of Obstetricians and Gynecologists (ACOG) Committee Opinions recommend that an initial evaluation of HMB, which may indicate a BD, include a complete blood count; serum

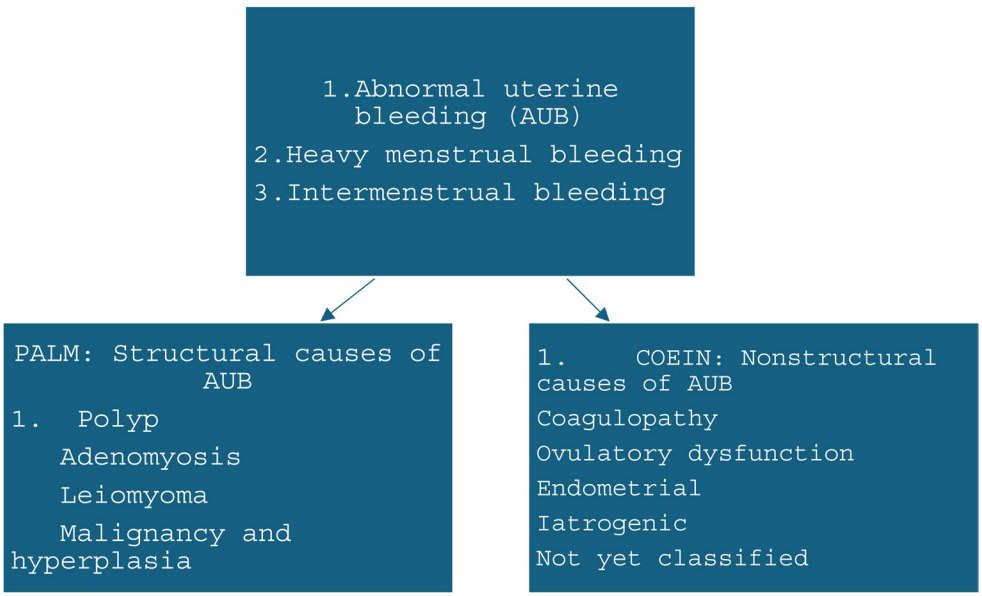


Fig. 1 Federation of international gynecology and obstetrics classification for causes of abnormal uterine bleeding: PALM-COEIN

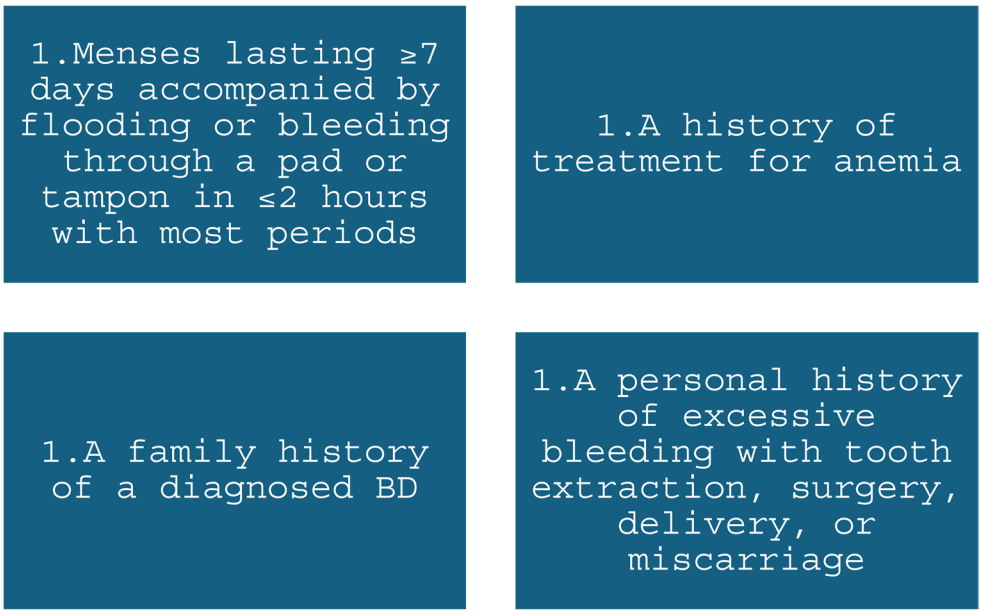


Fig. 2 Adolescents who report heavy menstrual bleeding and meet any of the four criteria should be screened for a bleeding disorder

Table 1 Thrombosis and haemostasis bleeding assessment tool (ISTH-BAT)

Aspect	Details
Purpose	To quantify bleeding symptoms and screen for inherited bleeding disorders
Domains (14)	Epistaxis, cutaneous bleeding, minor wounds, oral cavity, GI bleeding, hematuria, surgery, dental extraction, menorrhagia, postpartum hemorrhage, muscle hematoma, hemarthrosis, CNS bleeding, other
Scoring (per domain)	0–4 (CNS: 0, 3, 4)
Score meaning	0: none; 1: mild; 2: medical attention; 3: intervention; 4: severe/transfusion
Total score	Sum of all domains = Bleeding Score (BS)
Abnormal cut-offs	Children (< 18 years, including adolescents) ≥ 3; Adult females ≥ 6
Interpretation	A high score indicates likely inherited BD; prospective use recommended in adolescents with HMB
Limitations	Less sensitive for children/adolescents due to evolving phenotypes; not ideal for acquired disorders

ferritin; standard coagulation studies (prothrombin time [PT], activated partial thromboplastin time [aPTT], thrombin time, and fibrinogen level); and testing for VWD (von Willebrand factor [VWF] antigen, ristocetin cofactor activity, and factor VIII [FVIII] levels) [6, 15].

Second-tier testing is reserved for patients with a significant bleeding history, persistent bleeding despite treatment, or nondiagnostic initial results, with particular attention to identifying platelet dysfunction. Consultation with a hematologist is recommended when an additional evaluation is being considered. Extended coagulation factor assessment may include quantification of factors II, V, VII, VIII, IX, X, XI, and XII. In addition, although an initial bleeding workup may be normal, some patients with connective tissue disorders such as Ehlers–Danlos syndrome may exhibit abnormal platelet aggregation [16].

Early recognition of BDs can significantly reduce hospitalizations and transfusion rates, improve quality of life, and prevent long-term adverse consequences. However, large cohort studies report that less than 25% of adolescents undergo appropriate diagnostic testing when first presenting with HMB [17, 18].

Bleeding Disorders

VWD represents the most prevalent inherited BD, occurring in approximately 1% of the general population, and is identified in more than one-third of adolescents who present with HMB [19]. Initial screening for VWD includes measurement of VWF antigen (VWF: Ag), VWF ristocetin cofactor activity (VWF: RCo), FVIII activity, and evaluation of VWF multimers [20]. A cost–utility analysis of VWD screening in adolescents with HMB demonstrated that, despite upfront costs, screening is cost-effective. This benefit is largely driven by the prevention of future bleeding complications, particularly in cases where VWD may be masked by hormonal contraceptive use [21].

VWD is classified into three main types. Type 1, the most common, accounts for approximately 75% of cases and typically results in mild to moderate bleeding. Type 2 consists of qualitative defects in VWF function. Type 3 is the rarest and most severe, characterized by an almost complete absence of VWF and very low FVIII levels, leading to significant bleeding symptoms. VWF: Ag and VWF: RCo levels < 0.30 IU/mL are considered diagnostic for VWD, whereas levels between 0.30 and 0.50 IU/mL are categorized as low VWF

[22]. VWD testing should be performed twice, with a minimum 4–6 week interval, to confirm the results. Although estrogen-containing hormonal contraceptives can increase VWF: Ag and VWF: RCo levels, current practice no longer recommends discontinuing beneficial hormonal therapy to evaluate for VWD, as combined oral contraceptives (COCs) typically contain relatively low estrogen doses (30–35 μ g) that do not preclude testing [23]. Acute bleeding episodes and stress can also increase VWF antigen and activity levels. Despite these physiologic fluctuations in VWF levels, testing for VWD can still identify most affected patients, even during an episode of acute HMB [24]. Although VWD is most commonly linked to HMB in adolescents, rare BDs like factor VII deficiency should also be considered in those with significant bleeding symptoms [25].

Adolescents with a family history of hemophilia should be assessed for deficiencies in FVIII or factor IX, corresponding to hemophilia A and B, respectively. Other rare coagulation factor deficiencies such as factors II, V, X, XI, and XII may also present with HMB and are typically inherited in an autosomal recessive pattern. Initial screening with PT and aPTT is useful for guiding further evaluation of these deficiencies.

Among adolescents with HMB, the most frequently encountered PFD is immune thrombocytopenic purpura, an acquired condition characterized by autoantibody-mediated platelet destruction leading to thrombocytopenia [26]. The primary inherited PFDs in this population are Glanzmann thrombasthenia and Bernard–Soulier syndrome, both of which are typically identified through specialized platelet aggregation testing. Several studies indicate that PFDs play an important role in women with HMB, with prevalence rates ranging from 2 to 47% [27]. One study found that nearly half of women presenting with HMB who did not have VWD were diagnosed with an inherited PFD [28]. The wide variation in reported prevalence of PFDs likely reflects multiple factors, including limited access to hematology specialists and the high cost or limited availability of testing.

Management of Adolescents With Bleeding Disorders

Among adolescents with BDs, HMB is the most frequently reported symptom, affecting an estimated 75–80% of individuals [6]. The goals of treating HMB are to improve quality of life, restore and maintain normal hemoglobin levels, and prevent transfusion-requiring or life-threatening hemorrhage. When available, patients with BDs should be referred to multidisciplinary clinics that offer coordinated care from gynecologists, hematologists, and social workers. This multidisciplinary team improves convenience and continuity of care for patients and their families [29, 30]. Adolescents diagnosed with a BD should be counseled to avoid medications that impair platelet adhesion such as aspirin and other nonsteroidal anti-inflammatory drugs unless specifically recommended by a hematologist.

As adolescents with known BDs enter puberty, worries about excessive menstrual bleeding and its impact on daily functioning and quality of life often increase for both patients and caregivers. Providing anticipatory guidance before menarche and a proactive plan for recognizing and managing potential HMB are essential. Therefore, adolescents with known BDs may need their first reproductive health visit earlier than the standard ACOG recommendation for all patients age 13–15 [31].

Hemorrhagic corpus luteum and associated hemoperitoneum from cyst rupture can also be a gynecologic manifestation of an underlying BD. For individuals who experience frequent hemorrhagic ovarian cysts, systemic hormonal contraception may help prevent recurrence [6].

Management of Acute HMB

In adolescents who are hemodynamically stable and have only mild to moderate anemia (hemoglobin > 8 g/dL), management can be initiated on an outpatient basis with iron therapy and appropriate hormonal treatment. Adolescents who present with hemodynamic instability or active HMB should be hospitalized, receive volume resuscitation with crystalloid, and undergo blood typing and crossmatching to prepare for potential transfusion needs. However, every effort should be made to avoid blood transfusion, particularly in generally healthy adolescents, as they typically respond rapidly to medical therapy. Transfusion decisions should be guided by clinical indicators such as hemodynamic status or persistent active bleeding rather than hemoglobin values alone. When transfusion is warranted, hemodynamic status should be reassessed after each unit of packed red blood cells [6].

For adolescents without contraindications to estrogen, acute bleeding control may be achieved with 25 mg intravenous conjugated estrogen given at 4–6-hour intervals or with oral monophasic COCs containing 30–50 µg of ethinyl estradiol (EE_2) administered every 6–8 h until cessation of bleeding [20]. See Table 2.

Estrogen should be given along with antiemetics. Intravenous conjugated estrogen is usually administered for at least 24 h or until bleeding resolves, followed by a COC tapering regimen [15]. There are insufficient data directly comparing the timing of bleeding cessation between intravenous estrogen and high-dose COCs. Both approaches are generally effective, with bleeding control typically achieved within 24–48 h. Intravenous estrogen is usually

Table 2 Management of Acute HMB

Intravenous Regimens	Oral Regimens
Conjugated equine estrogen: 25 mg every 4–6 h for 24 h	COCs containing 30–35 µg EE tapering regimen
Tranexamic acid: 10 mg/kg: (max 600 mg) every 8 h	Medroxyprogesterone (10–20 mg every 6–12 h)
Aminocaproic acid: 100–200 mg/kg (max 30 g/d) every 4–6 h	Norethindrone acetate (5–10 mg every 6 h)
	Tranexamic acid: 1300 mg three times per day
	Aminocaproic acid: 100–200 mg/kg (max 30 g/d) every 4–6

Adapted from Borzutzky et al. [9]

reserved for patients with severe anemia, those requiring rapid control of bleeding, or those who have failed outpatient oral hormonal therapy [6, 9]. In a recent study examining adolescents hospitalized for severe anemia (hemoglobin ≤ 8 g/dL) secondary to acute abnormal uterine bleeding, those treated with combined intravenous conjugated equine estrogen and high-dose COCs had a significantly longer hospital stay and higher rates of nausea requiring antiemetic therapy compared with patients managed with high-dose COCs alone [32].

When prescribing COCs, monophasic formulations containing 30–50 micrograms of EE_2 are preferred since they provide more reliable endometrial stabilization than lower-dose options. Because no single tapering regimen is universally recommended, therapy should be continued at the dose required to keep bleeding suppressed until the patient's hemoglobin improves to a level that would allow her to tolerate a withdrawal bleed. A 2022 retrospective study [33] found that higher-dose tapering regimens of combined oral contraceptives (COCs)—typically starting with multiple pills daily (e.g., 2–3 pills of a standard 30–35 mcg EE_2 formulation, equaling 60–105 mcg EE_2) and gradually reducing over several days to weeks—do not decrease the time to resolution of acute heavy menstrual bleeding (HMB) in adolescents compared to standard-dose regimens using ≤ 35 mcg EE_2 per day without tapering.

For adolescents who cannot use estrogen because of contraindications or intolerance, progesterone-only regimens may provide effective bleeding control. Commonly employed options include oral medroxyprogesterone (10–20 mg every 6–12 h) and norethindrone acetate (5–10 mg every 6 h) [20]. In the acute setting, these can be prescribed as a taper initially and then reduce to daily once bleeding has stopped. Unlike most other progestins, norethindrone acetate (NETA) undergoes partial conversion to EE_2.

The pharmacokinetics of NETA (commonly known as Aygestin) are not fully elucidated, and individual metabolism can vary significantly, influencing its conversion to EE. That said, published data provide some estimates: Approximately 1 mg of NETA yields about 4 µg of EE2, so a typical 5 mg dose offers estrogen exposure comparable to a 20 µg EE_2 combined oral contraceptive (COC) (6). More recent studies indicate that a 20 mg dose of NETA produces an estrogen effect similar to roughly 30 µg of EE_2 [34].

The clinical implications of NETA's conversion to EE_2 remain unclear with respect to VTE risk. Nonetheless, awareness of this potential risk is important, given that NETA multidose tapers are frequently used as an alternative to estrogen-containing therapies in patients with estrogen contraindications.

If bleeding persists or shows minimal improvement after 24–48 h, adjunctive therapy such as tranexamic acid (TXA) may be added, and escalation of care, including hematology consultation, should be considered if not already involved. While TXA has been associated with a theoretical risk of thrombosis, studies have not demonstrated an increased incidence of thromboembolic events [35]. Oral TXA is administered at a dose of 1.3 g three times daily for 5 days. Aminocaproic acid (AMICAR) may be used as an alternative; 100–200 mg/kg (max 30 g/d) every 4–6 h [9]. Intravenous TXA is generally reserved for adolescents with severe bleeding, with weight-based dosing of 10 mg/kg (up to a maximum of 1000 mg) administered every 8 h [36]. In adolescents with specific clotting factor deficiencies, management may necessitate administration of plasma-derived or recombinant clotting factor replacement. Desmopressin increases VWF and FVIII and is useful for treating HMB in VWD, as well as in some PFDs and hypermobility syndromes [37].

If bleeding persists despite intensive medical therapy, uterine tamponade with a 30 cc Foley catheter offers an efficient and reversible option for this population. The catheter can remain in place for 12–24 h and removed with gradual deflation [38]. Antibiotics may be administered for infection prevention while the Foley balloon is in place, although supporting evidence is limited. When severe bleeding necessitates further evaluation, an examination under anesthesia may be required. Hysteroscopy can be useful in patients with suspected intrauterine pathology or when tissue sampling is indicated. Additionally, placement of a levonorgestrel-releasing intrauterine device (LNG-IUD) may be considered at the time of the procedure for long-term management, but patients must be informed of the higher expulsion risk in the setting of HMB. Because of potential impacts on future fertility, surgical interventions are generally avoided in adolescents. If tamponade fails and bleeding becomes life-threatening, procedures such as dilation and suction curettage, uterine artery embolization, or hysterectomy should be reserved as true last-resort options [15].

Management of Chronic HMB and Maintenance Therapy

Despite the availability of various hormonal and nonhormonal treatment modalities, the literature remains limited regarding optimal management of HMB in patients with BDs. Failure of an initial therapy for HMB is not uncommon. In a retrospective review of adolescents with BDs, 53% did not respond to first-line treatment. Subsequent management more often required a combination of hormonal and nonhormonal therapies [39].

Hormonal Treatments

Maintenance hormonal therapy may include combined hormonal contraceptives (CHCs; e.g., pill, patch, or vaginal ring) or oral, injectible, or implantable progestins. Many patients undergo various treatment changes, with an increasing proportion choosing to use the LNG-IUD [40].

In adolescents with BDs, continuous or extended-cycle use of CHCs has been associated with more favorable bleeding patterns than traditional monthly cycling [41]. Although CHCs containing lower doses of EE_2 (10–20 µg) produce lighter withdrawal bleeding with monthly or extended-cycle use, they are more likely to cause breakthrough bleeding, especially in adolescents with BDs, which may necessitate switching to higher-dose formulations. Consistent adherence to medications taken on a daily, weekly, or monthly schedule may pose challenges for adolescents. The transdermal patch and vaginal ring do not appear superior to oral contraceptive pills, and despite higher perceived ease of use with the ring, continuation and perfect use remain suboptimal across short-acting methods [42, 43].

When estrogen-containing methods are contraindicated or fail, progesterone-only regimens such as oral or injectable progestins, an implant, or a LNG-IUD represent effective alternatives for maintenance therapy. Reports indicate that oral NETA at 5–10 mg/day may be more effective than COCs for treating HMB in individuals with BDs [20]. In a retrospective chart review of adolescents with HMB seen in a multidisciplinary hematology-adolescent gynecology clinic, NETA 5–10 mg/day achieved a high rate of menstrual suppression (83%), second only to the LNG-IUD (89%). In contrast, menstrual control was observed in only 42% of those using COCs [13]. In 2019, a randomized controlled trial compared COCs with NETA for managing late-cycle breakthrough bleeding or delaying menses. No patients receiving NETA experienced spotting, whereas 40% of patients in the COC group reported spotting or irregular bleeding. Patient satisfaction was also higher in the NETA group (80%) [44].

Depot medroxyprogesterone acetate (DMPA) induces amenorrhea in up to half of users and is usually administered every 12 weeks. Shortening the interval to every 4–10 weeks can help control heavy breakthrough bleeding, after which the standard 12-week schedule may be resumed [45]. Subcutaneous medroxyprogesterone acetate provides an alternative for adolescents in whom intramuscular injections are contraindicated due to hematoma risk. Although the etonogestrel implant is an effective contraceptive, it is not recommended as first-line therapy for HMB in adolescents with BDs because of frequent breakthrough bleeding and fewer than 20% of users achieve amenorrhea [46].

The LNG-IUD has been shown to be an effective option for improving HMB and anemia in adolescents with BDs, and is increasingly being used in this population [16, 47]. Current evidence on LNG-IUD use in individuals with BDs is limited to the 52 mg device, with no data available for lower-dose formulations [48]. In one prospective study of 73 adolescents with BDs, the LNG-IUD had the highest success rate (89%) [13]. LNG-IUD use in this population has been associated with high rates of amenorrhea (up to 60%) and long-term continuation [16, 47]. Slightly higher expulsion rates were reported in the first 30 days, likely related to heavy bleeding following insertion [16, 47]. In a recent retrospective study, no early expulsions due to excessive bleeding occurred among 24 LNG-IUD insertions when patients continued their prior hormonal therapy for at least 30 days after placement [49].

While there is limited literature on complications during IUD insertion in this cohort, collaboration with a hematologist is recommended to enhance periprocedural hemostasis and reduce bleeding risk. In a recently published systematic review and thematic synthesis of 13 studies involving 893 participants, the LNG-IUD was identified as highly effective for managing HMB in individuals with inherited BDs. Treatment with the LNG-IUD, and subsequently with TXA or desmopressin when required, commonly achieved amenorrhea [50].

Nonhormonal Treatments

Nonhormonal options for HMB in adolescents with BDs include administration of TXA, aminocaproic acid, desmopressin, and other clotting factor replacement. Both TXA and desmopresin have been shown to cause statistically significant decreases in HMB and improved quality of life when used during menses [51].

TXA is endorsed by the ACOG Committee on the Screening and Management of BDs in Adolescents with HMB as an important therapeutic option. Studies indicate that 27–66% of adolescents with BDs and HMB require a combination of hormonal and nonhormonal therapies, including

antifibrinolytics such as aminocaproic acid and TXA [26, 39]. Randomized controlled trials have demonstrated that TXA reduces menstrual blood loss by 34–59% compared to placebo [52]. In a prospective randomized crossover study of postmenarchal adolescents, both CHCs and TXA improved menstrual blood loss and quality-of-life scores, with TXA producing fewer adverse effects [50]. TXA may be given as two 650 mg tablets (1300 mg) three times daily for up to five days during menses, not exceeding a total daily dose of 3900 mg. A recent randomized crossover trial in patients with VWD found that TXA improved bleeding significantly more than recombinant VWF [53].

Evaluating all patients with HMB for iron deficiency may significantly improve clinical symptoms and help prevent anemia through timely iron supplementation [54]. However, studies show that among adolescents with abnormal uterine bleeding evaluated in emergency settings, only 6.8–8.9% undergo assessment for iron deficiency [55, 56]. Providing iron replacement therapy is important for adolescents with anemia or iron deficiency, since inadequate iron stores can contribute to fatigue and cognitive difficulties, even when hemoglobin levels are normal [6]. A daily elemental oral iron dose of 60–120 mg is recommended, with newer evidence suggesting that once-daily or alternate-day dosing enhances absorption by reducing hepcidin-mediated inhibition [57].

Venous Thromboembilism (VTE)

VTE, which includes DVT and PEs, is a rare but serious adverse event in children and adolescents. When VTEs do occur in the youngest population, it is most common in children under 1 year old and then peaks again in the adolescent years [58]. Data suggests a background incidence of pediatric VTE of approximately 0.07–0.49 in 10,000 children [59]. In female adolescents, the incidence of VTE is approximately 2–3 in 10,000 [59, 60]. Typical risk factors for VTE include obesity, immobility, recent surgery, autoimmune conditions, inherited and acquired thrombophilias, pregnancy, tobacco use, contraception use, infections, and malignancy. Some conditions unique to the pediatric population are known to increase VTE risk, such as congenital heart disease and congenital venous malformations [61].

Hormonal Contraception and VTE Risk

Female adolescents are commonly prescribed hormonal medications for contraception and menstrual management, often for dysmenorrhea and abnormal menstrual bleeding. CHCs that contain EE_2 and progestins are some of the most frequently prescribed medications in this cohort. These can be prescribed in different forms including as a COC pill, transdermal patch, or vaginal ring. By increasing hepatic production of clotting factors and decreasing anticoagulant proteins, estrogen promotes a procoagulant state, which increases VTE risk, especially in patients with additional risk factors.

While the risk of contraception-associated VTE is well-established as less than 1 per 1000 exposure years in younger patients- meaning it affects fewer than 0.1% of users annually, those younger than age 20 account for approximately 5.9–9.6% of total VTE events in large population studies [62]. COCs have shown a three-six-fold increase in VTE risk [60, 62], but this translates to small absolute increase (e.g. from 2 per 10,000 women-years in non-users to 4–6 per 10,000 in users). Patches may confer similar or slightly higher risks, with pharmacokinetic studies of the CHC patch demonstrating approximately 60% higher plasma- estrogen exposure than standard equivalent COCs, potentially explaining modestly elevated VTE rates [63, 64]. For example, overall VTE rates with the CHC patch in those aged 15–29 are 5.3 per 10,000 women-years compared to 4.2 per 10,000 for COCs [65]. Overall, the risk of VTE associated with CHCs remains substantially lower than that observed during pregnancy (5–20 per 10,000 woman-years) and particularly during the postpartum period, when the risk is highest (approximately 40–116 per 10,000 woman-years) [66, 67].

Standard estrogen-dose COCs contain 30–35 mcg of EE_2. Many newer COCs have "low-dose" options, including those that contain $\leq$ 20 mcg of EE_2. These options have often been thought to decrease the risk of thrombotic events; however, data regarding thrombosis outcomes comparing 20 mcg to 30–35 mcg is limited [62]. Some data have demonstrated that lower EE_2 levels ($\leq$ 20 mcg) can impact rates of bone accrual in adolescents, which is important for long-term bone health [68]. Therefore, lower-dose EE_2 COC options may not be as beneficial as previously thought.

It is also important to consider the progestin component of CHCs when considering VTE risk.

While CHCs containing newer progestins (such as desogestrel, gestodene, or drospirenone) have been associated with a higher relative risk of VTE compared to those with levonorgestrel, this corresponds to a small absolute increase, as the overall incidence remains rare (e.g., from about 5–7 per 10,000 woman-years to 9–12 per 10,000) [69].

Progesterone-only contraceptive methods can also increase VTE risk, in those with underlying risk factors and when given in high doses. While injectable DMPA has been shown to be associated with a two- to three-fold increased relative risk of VTE in limited studies, this corresponds to a small absolute increase, as the overall incidence remains rare (e.g., from about 1–2 per 10,000 woman-years in non-users to 3–6 per 10,000 in users) [70]. An increased VTE risk with high-dose oral norethindrone acetate—due to its

systemic conversion to EE_2—has also been demonstrated [34], though again, the absolute risk elevation is modest. This conversion is important to consider, especially given that progesterone-only options are often considered to be safer in those with underlying VTE risk or those with a history of VTE.

Hormone use is rarely the only risk factor in adolescents who develop VTE. In fact, nearly 96% of adolescents who develop VTE have at least one other identifiable risk factor and 59.6% have four or more risk factors [58]. The most common additional risk factor, obesity, was present in nearly 50% of contraceptive-using adolescents who developed VTE [59–61].

Inherited and Acquired Thrombophilias

Thrombophilias are disorders that increase an individual's underlying clotting risk, typically through VTEs. Thrombophilias can be inherited or acquired. It is important to gather a personal and family history when assessing possible thrombophilias and risk factors for VTE development.

Inherited thrombophilias are secondary to genetic mutations in clotting factors or anticoagulant proteins. The most common inherited thrombophilias are Factor V Leiden (FVL), Prothrombin G20210A (also called prothrombin gene mutation or PGM), Protein S deficiency (PS), Protein C deficiency (PC), and Anti-Thrombin (AT) deficiency [71]. See Table 3. These can be further classified into low- and high-risk thrombophilias based on the underlying likelihood of developing a VTE. Low-risk thrombophilias (e.g., heterozygous FVL and PGM) have a two-three-fold increased risk of VTE [72]. High-risk thrombophilias (e.g., AT deficiency and homozygous FVL) have a 12-fold and up to 80-fold increased risk of VTE respectively [71].

While the elevated risk of venous thromboembolism (VTE) associated with combined hormonal contraceptives (CHCs) is a valid concern, routine screening for thrombophilias (such as factor V Leiden [FVL] or other inherited clotting disorders) before initiating contraception is generally not recommended [73]. This is largely due to cost-effectiveness considerations. For instance, a 1990s cost-analysis study estimated that identifying over 92,000 FVL carriers and preventing them from using CHCs would be required to avert just one VTE-related death, at a total cost exceeding $300 million [74]. Similarly, a European study on cost-effectiveness found that universal thrombophilia screening would cost more than €200,000 to prevent a single VTE episode; this figure dropped to about €80,000 when limited to individuals with a personal or family history of VTE [75]. Based on these analyses, screening for all patients is not advised. However, targeted screening may be reasonable for those with a significant personal or family history of VTE, or a known family history of thrombophilia (e.g., FVL or prothrombin gene mutation). As a practical and cost-effective alternative to genetic testing, many providers opt to avoid estrogen-containing contraceptives altogether in high-risk individuals—such as a strong family history of VTE (e.g., first-degree relatives affected at a young age) or confirmed inherited thrombophilias—favoring progesterone-only options or non-hormonal methods instead.

Table 3 Most common inherited thrombophilias

Factor V Leiden (FVL)
Prothrombin G20210A
Protein S deficiency (PS)
Protein C deficiency (PC)
Anti-Thrombin (AT) deficiency

Acquired thrombophilias are typically secondary to other medical conditions, environmental factors, or autoimmune conditions. The most notable examples are antiphospholipid syndrome (APS) and lupus anticoagulant, both of which are categorized as autoimmune conditions. APS often presents with VTE events and/or negative pregnancy outcomes, such as recurrent miscarriage or early onset preeclampsia. It is important to assess a family history in adolescents seeking contraception, as even APS and lupus are thought to have a hereditary component [76]. The prevalence of these types of acquired thrombophilia in adolescents is not well known and requires more research; however, the prevalence of positive antibodies in children with VTE is as high as 24% [73, 77].

Contraception in Those With a Personal History of VTE

Adolescent patients are often told to discontinue their contraceptives after first VTE diagnosis out of caution and concern for recurrence. Not all contraceptive methods confer an increased risk for VTE. It is essential to offer alternative methods, as immediate discontinuation can put these patients at risk for unintended pregnancy. A recent study found that 7.9% of adolescents and young adults with VTE became pregnant within two years after diagnosis, with two pregnancies occuring while patients were on warfarin, a known teratogenic medication [60]. All adolescents should be counseled and offered appropriate contraceptive methods to regardless of their recurrent VTE risk, because pregnancy itself carries a 10-fold higher VTE risk than any contraceptive method [59]. Additionally, the postpartum state presents an even higher risk, an approximately 20–25-fold increase [78].

The Centers of Disease Control and Prevention Medical Eligibility Criteria for Contraceptive Use (US MEC) is a resource that assigns risk scores to contraceptive options in the setting of different medical conditions. The US MEC recommends against CHCs in those with a personal

history of VTE, designating this method as one where risk outweighs the potential benefit, or that is unacceptable entirely [79].

Newer data suggests the progesterone-only method DMPA confers a higher VTE risk than previously assumed [70]. DMPA is therefore not recommended in patients with a history of VTE and high risk of recurrence who are not on anticoagulation regimens [79]. Other progesterone-only methods, including progesterone-only pills and progestin-only implants are considered generally safe, with benefits outweighing the potential risks [79].

The 2024 CDC U.S. Medical Eligibility Criteria (US MEC) updated the classification for hormonal contraceptives in patients with current or history of DVT/PE who are on therapeutic anticoagulation, changing it from category 3–4 (2016) to category 2–3. In this population, all hormonal methods—including combined hormonal contraceptives, progestin-only pills, depot medroxyprogesterone acetate, implants, and levonorgestrel IUDs—are now classified as category 2 (advantages generally outweigh risks), except combined hormonal contraceptives, which are category 3. This change is supported by evidence showing no increased risk of recurrent venous thromboembolism with hormonal contraceptive use during therapeutic anticoagulation [79].

Menstrual Management in Anticoagulated Patients

Patients with active VTE and those with a high risk of VTE recurrence are often treated with anticoagulation regimens such as enoxaparin, heparin, warfarin, and fondaparinux. Discontinuation of hormonal methods, regardless of initial indication for prescribing, will often put adolescent patients at risk of HMB secondary to anticoagulation [60].

One study in adolescent patients using anticoagulation treatment reported a 76% incidence of HMB [80]. In addition, this study found anemia in 43% of those patients with HMB, 50% of which required blood transfusions for management [80]. Due to the high rates of anemia in adolescents using anticoagulation therapy, it is advised to recommend safe hormonal medications for prevention of HMB [60].

Another observed potential consequence of anticoagulant medication in adolescents is a risk of developing hemorrhagic ovarian cysts. 7% of adolescents who were started on anticoagulation medication developed symptomatic cysts, 40% of which required surgical intervention for bleeding control and 20% of which required blood products [80]. Ovulation-suppressing combined hormonal contraceptives reduce the risk of functional ovarian cysts and related complications, including rupture and hemoperitoneum. In patients receiving anticoagulation, they may be considered in appropriately selected individuals to help mitigate the risk of hemorrhagic cyst formation. Although specific guidelines are lacking, evidence from adolescents with bleeding disorders supports also the use of ovulation-suppressing progestin-only methods, such as implants or depot medroxyprogesterone acetate, for prevention of recurrent hemorrhagic cysts [6, 81].

While VTE in the adolescent is a rare event, it can result in serious outcomes and other long term complications. Therefore, it is important to assess personal and family history VTE risk prior to initiating hormonal contraception. It is not recommended that all adolescents be routinely screened for hereditary thrombophilias prior to initiating hormonal contraceptives. Most adolescents who develop VTE while using CHCs have multiple risk factors, often four or more, with obesity being the one of the most common contributory factors. The US MEC is an essential resource for providers to effectively assess the safety profile of contraceptives in patients with a personal history of VTE or those with known conditions that can increase risk.

Conclusion

In adolescents with a high risk of venous thromboembolism (VTE) or a personal history of VTE not on anticoagulation therapy, estrogen-containing combined hormonal contraceptives (CHCs) should typically be avoided to reduce clotting risks, with progestin-only methods like IUDs, implants, or pills most frequently recommended instead. For sexually active teens in this group, counseling must balance these precautions against the fact that VTE risks during pregnancy and the postpartum period far exceed those of any hormonal contraceptive method. Ultimately, individualized counseling and treatment are essential for improving outcomes in adolescents with bleeding disorders and VTEs, optimizing menstrual management and effective contraception while prioritizing thrombotic safety. Future studies are needed to develop personalized approaches that address diverse clinical needs and support long-term reproductive health, and multidisciplinary teams play a key role in enhancing evaluation, treatment, and ongoing management for this population.

Key References

American College of Obstetricians and Gynecologists. ACOG Committee Opinion No. 785, Screening and Management of Bleeding Disorders in Adolescents With Heavy Menstrual Bleeding: Correction. Obstet Gynecol. 2023;141(1):228. doi: https://doi.org/10.1097/AOG.0000000000005029.

- The ACOG Committee Opinion recommends that adolescents with HMB be screened for underlying BDs, such as VWD, to facilitate timely diagnosis and management. It also emphasizes the importance of a multidisciplinary approach involving hematology, gynecology, and primary care to improve outcomes.

Borzutzky C, Jaffray J. Diagnosis and Management of Heavy Menstrual Bleeding and Bleeding Disorders in Adolescents. JAMA Pediatr. 2020;174(2):186−94. doi: https://doi.org/10.1001/jamapediatrics.2019.5040.

- This well published study reviews how to clinically assess, order laboratory testing, and consider treatment options for adolescents with HMB.

Lacy B, French A, Berger-Chen S, Shah-Bruce M, Haamid F. NASPAG Clinical Consensus: Use of Tranexamic Acid in the Treatment of Heavy Menstrual Bleeding. J Pediatr Adolesc Gynecol. 2025;38(4):452-7. doi: https://doi.org/10.1016/j.jpag.2025.02.008.

- This clinical consensus provides current and valuable information on the use of TXA as a treatment modality for HMB in this age group. It also offers useful insights into the efficacy and safety of TXA when used as monotherapy or in combination with CHCs.

Huguelet PS, Laurin JL, Thornhill D, Moyer G. Use of the Levonorgestrel Intrauterine System to Treat Heavy Menstrual Bleeding in Adolescents and Young Adults with Inherited Bleeding Disorders and Ehlers-Danlos Syndrome. J Pediatr Adolesc Gynecol. 2022;35(2):147−52 e1. doi: https://doi.org/10.1016/j.jpag.2021.11.002.

- Limited evidence currently exists regarding the use of the LNG-IUD in adolescents with inherited BDs. In line with its increasing use due to high rates of amenorrhea and strong long-term continuation, these data represent important information regarding safety and efficacy in this special population.

Maher KN, Quint EH, Weyand AC. Management of Contraception in Adolescent Females With Hormone-Related Venous Thromboembolism. J Adolesc Health. 2022;71(1):127−31. doi: https://doi.org/10.1016/j.jadohealth.2022.02.009.

- This article discusses safe contraceptive options for adolescent females with a history of hormone-related VTE. It recommends not avoiding contraception in patients with VTE as pregnancy can still occur (and with a much higher risk of VTE). They recommend non-hormonal or progestin-only contraceptives as preferable alternatives to manage contraception in this population.

Middeldorp S, Nieuwlaat R, Baumann Kreuziger L, Coppens M, Houghton D, James AH, et al. American Society of Hematology 2023 guidelines for management of venous thromboembolism: thrombophilia testing. Blood Adv. 2023;7(22):7101-38. doi: https://doi.org/10.1182/bloodadvances.2023010177.

- The 2023 American Society of Hematology guidelines provide evidence-based recommendations for thrombophilia testing in the management of VTE.

Nguyen AT, Curtis KM, Tepper NK, Kortsmit K, Brittain AW, Snyder EM, et al. U.S. Medical Eligibility Criteria for Contraceptive Use, 2024. MMWR Recomm Rep. 2024;73(4):1-126. doi: https://doi.org/10.15585/mmwr.rr7304a1.

- This provides updated, evidence-based guidelines on the safety of various contraceptive methods for individuals with specific medical comorbidities. These criteria are designed to assist healthcare providers in making informed contraceptive decisions for patients.

Pennesi CM, Quint EH, Rosen MW, Compton SD, Odukoya EJ, Weyand AC. Outpatient Management of Heavy Menstrual Bleeding in Adolescent and Young Women with Inherited Platelet Function Disorders. J Pediatr Adolesc Gynecol. 2020;33(5):489−93. doi: https://doi.org/10.1016/j.jpag.2020.06.019.

- This retrospective study provides useful information on treatment options for HMB in girls with inherited PFDs, a population for which data are scarce and management is challenging despite ongoing follow-up and treatment adjustments.

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Declarations

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