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VTE and anticoagulation in menstruating women

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ABSTRACT

Women of childbearing potential have a high prevalence of venous thromboembolism (VTE) due to high estrogen states, such as pregnancy and the use of estrogen-containing contraceptives. Abnormal uterine bleeding (AUB) affects up to two-thirds of menstruating women on anticoagulation (AC), and can severely impair a woman's quality of life. Rates of heavy menstrual bleeding (HMB) and other forms of AUB including inter-menstrual and postmenopausal bleeding are consistently underreported in the original clinical trials utilizing AC. VTE can occur at any time in a woman's life, and the aim of this review article is to discuss the current landscape of literature on AUB for women on AC, VTE and AC in women of child bearing potential, planning for pregnancy while on AC, VTE during pregnancy, and considerations for VTE risk in postmenopausal women. This survey of the current literature may offer data for providers to consider while making clinical decisions on the duration of and appropriate choice of anticoagulation.

Menstruation is a routine and natural aspect of the female life cycle that can become pathologic. Abnormal uterine bleeding (AUB) is defined as bleeding of abnormal quantity, frequency, and/or duration. Abnormal bleeding during and throughout the menstrual cycle can affect up to 30% of pre-menopausal women and has a significant, negative impact on quality of life. AUB includes heavy menstrual bleeding (HMB) that can be due to functional abnormalities, anatomic etiologies, systemic disorders, or medication effect. Taking a thorough menstrual, obstetric and bleeding history is of utmost importance prior to initiating medication that can precipitate further bleeding, such as oral anticoagulants for the treatment of venous thromboembolism (VTE).

Notably, women of reproductive age are disproportionally affected by VTE compared to males of the same age range [1,2]. The use of anticoagulants (AC) for the treatment of VTE can transform normal periods into heavy ones and heavy ones into medical emergencies. The standard measures utilized in the assessment of bleeding outcomes in large randomized clinical trials of oral anticoagulants (OACs) were not designed to quantify HMB and thus grossly underestimate the incidence. Post-hoc analysis of data from these trials as well as a handful of observational studies, primarily retrospective, have been published but unfortunately utilize discrepant definitions of AUB [3,4]. The best available data, from observational prospective trials suggest that 70% of menstruating individuals may suffer AUB while on OACs.

1. Heavy menstrual bleeding and abnormal uterine bleeding

Historically, heavy menstrual bleeding was defined as menstrual blood loss (MBL) of >80 mL/cycle or pictorial blood loss assessment chart (PBAC) score >100 [5,84]. The PBAC is a semi-quantitative, inexpensive method used to assess blood loss utilizing a visual, graded series of tampons or sanitary napkins. It is often used in clinical trials and allows for patients to record her used feminine items and the degree in which they are blood stained [5,84]. A more modern definition is excessive menstrual blood loss (MBL) that interferes with a woman's physical, emotional, social wellbeing and quality of life. Randomized controlled studies of oral anticoagulants do not include AUB as an outcome, instead relying on the International Society of Hemostasis and Thrombosis (ISTH) major and clinically relevant nonmajor bleeding (CRNMB) definitions. As determined by ISTH, major bleeding (MB) in non-surgical patients is defined as fatal bleeding, and/or symptomatic bleeding in a critical area or organ, or bleeding causing a fall in hemoglobin level of 20 g/L or more, or leading to transfusion of two or more units of whole blood or red cells [6]. Clinically relevant nonmajor bleeding is defined as an acute or subacute clinically overt bleed that does not meet the criteria of a major bleed yet continues to prompt a

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clinical response. In this definition by the ISTH, one of the following criteria must be met: a hospital admission for bleeding, a provider-guided medical or surgical treatment for bleeding or a change in antithrombotic therapy (including interruption or discontinuation of anticoagulation) [6].

AUB, which includes HMB as well as other differences in frequency, regularity or duration of bleeding, is a common, pathologic gynecologic disorder which affects up to one-third of all women [7,8]. AUB accounts for more than 3 million ambulatory care visits annually and for more than 20% of all visits to obstetricians and gynecologists [9]. Unfortunately, due to many factors, potentially including period taboos and a lack of education around normal menses, many women will only be diagnosed with AUB after they develop iron deficiency with or without anemia. Although AUB does not frequently cause severe morbidity or mortality, quality of life is significantly reduced in women suffering from AUB [7]. Healthcare related quality of life (HRQoL) surveys demonstrate that women with AUB ranked below the 25th percentile for the general female population within the same age range. Additionally, conservative estimates on healthcare expenditure, direct and indirect economic effect of AUB was thought to be between $1–12 billion annually [7]. This estimate does not take into account indirectly related expenses that could be related to time off work and economic burden [7]. The treatment for AUB is directed towards the underlying pathologic abnormality and includes medical and surgical options.

Medical therapies for AUB primarily consist of hormonal therapy and estrogen-progestin oral contraceptives are considered a first-line therapy, with the added benefit of providing contraception in many cases [10]. For patients who prefer to avoid hormonal therapies, anti-fibrinolytic therapies such as tranexamic acid are another first-line option [11]. Non-steroidal anti-inflammatory drugs (NSAIDs) effectively reduce blood loss per cycle, despite known interference with platelet function [12]. Generally, it is recommended to attempt medical therapy for at least three months prior to considering invasive procedures such as endometrial ablation, uterine artery embolization or hysterectomy, all of which have the potential to cause morbidity with any future pregnancy and/or result in infertility [13]. It is estimated that approximately 25% of all hysterectomies are performed for AUB [13].

Menorrhagia and AUB are the most common cause of iron deficiency anemia in the developed world. Iron deficiency with or without anemia can reduce quality of life, impair concentration, decrease exercise capacity and tolerability and impair functional status. A retrospective analysis on the impairment of quality of life due to AUB demonstrates that the primary side effects of iron-deficiency anemia were self-reported weakness, fatigue, unexplained weight loss, mood swings and cognitive impairment [14]. Several European healthcare-quality-of-life (HRQoL) randomized controlled trials demonstrated that AUB primarily affects physical, emotional, sexual, work and daily productivity [15–20]. In fact, many demonstrated that women with AUB were below the 25th percentile of national norms of productivity in the United Kingdom [7]. HRQoL trials performed in the United States also demonstrated significant impairment in sexual functioning, psychiatric manifestations of depression, anxiety, adjustment and personality issues [21–29].

2. VTE and anticoagulation in women of child bearing potential

Many factors can increase the risk of VTE in women of childbearing potential, including the utilization of estrogen-containing contraceptives, nicotine use, obesity, hypertension, inflammatory states, malignancy, prior history of VTE, trauma, and thrombophilias. Balancing the risk of excessive bleeding in women with that of recurrent thromboembolic events can pose a challenge while on AC. In the setting of provoked VTE from high estrogen states, the duration of AC is 3 months. However, as found in the REVERSE trial, an individualized assessment is likely needed for all patients, particularly those with a high HERDOO2 score [67]. AC-associated HMB requires treatment, as early discontinuation or intermittent use of AC may precipitate further VTE (see Table 1).

Table 1
[30] Management of AUB in the context of OAC.

At OAC Initiation	>1 month OAC therapy remaining	<1 month of OAC therapy remaining
First Line:	**First Line:**	**First line:**
- Continue prescribed contraceptive - LNG-IUS - Select lower risk OAC	- LNG-IUS - Select lower risk OAC	- LNG-IUS - Observation/ supportive care
Second Line:	**Second Line:**	**Second Line:**
- Subdermal implant/ POPs/DMPA - Begin CHC	- Subdermal implant/POPs/ DMPA - If severe HMB: consider procedural intervention - Tranexamic acid	- Select lower risk OAC - Subdermal implant - Severe HMB: Tranexamic acid

Providers often discontinue hormonal therapy such as contraceptives at the time of a new VTE episode-a practice that frequently precipitates more severe HMB. For patients with known HMB who required OAC therapy, Table 2 below summarizes options and recommendations for HMB management [30]. We also recommend that prescribers of OACs to menstruating individuals obtain a thorough menstrual history first to evaluate for HMB, as well as routine laboratory workup with a complete blood count and ferritin to assess iron stores. In addition to being effective for the management of HMB, contraceptives are also crucial to prevent maternal morbidity due to recurrent, provoked VTE and the potential teratogenic effects of OACs. The first line therapy for any patient with HMB prior to or during OAC therapy for VTE is the levonorgesteral intrauterine system (LNG-IUS) and to utilize the lowest possible risk OAC. In the second line, subdermal implants, progestin-only pills (POPs) depot medroxyprogesterone acetate (DMPA), or combined hormonal contraceptives (CHCs) can also be utilized. DMPA and CHCs should be discontinued one month prior to discontinuing anticoagulation.

Rivaroxaban and apixaban are the most commonly utilized OACs [32]. The data on AUB and HMB associated with OACs is generally minimal due to the inadequacy of currently used outcome measures to capture these events, although retrospective analyses have attempted to address this issue. Retrospective data demonstrate that incidence of AUB may be as high as 73% in patients utilizing rivaroxaban, and that significant AUB may lead to dose modification, disruption of AC and a decreased treatment time period [31]. A retrospective analysis demonstrated that rivaroxaban was associated with HMB in approximately forty-five percent of subjects [31]. Apixaban and warfarin therapy were also associated with HMB in approximately one quarter of subjects [30]. A 2017 review and meta-analysis demonstrated that women receiving rivaroxaban had a twofold increased risk of AUB (RR 2.19; 95% CI, 1.64–2.69, $p < 0.0001$) as compared with women receiving VKAs; this increase was not demonstrated in women receiving apixaban or edoxaban [32]. Notably, women on rivaroxaban required more surgical and medical interventions for AUB [32]. Post hoc analyses of the RE-COVER and RE-MEDY trials also suggested that dabigatran carries a lower risk of uterine MB and CRNMB (4.7%) than warfarin (Table 2). AUB, including heavy and postmenopausal bleeding, also occurred more frequently in the warfarin arm (9.6%) [33–35]. A single-center study demonstrated that women on rivaroxaban who have HMB had a fivefold increased risk of recurrent VTE compared to women who didn't suffer from HMB, potentially due to challenges with adherence related to HMB [36]. This difference was not found among women on warfarin.

Original data from AC clinical trials did not clearly quantify AUB or HMB. As such, it can be assumed that AUB was likely underreported. Extension trials, cancer-associated VTE trials and observational studies have reported additional data on the incidence of AUB in menstruating

Table 2
Uterine CRNMB in AC trials.

Trial	Study design	Study drug/ comparator (maintenance dose)	Number of subjects	Uterine CRNMB, n (%)
Extended Therapy >6 months				
AMPLIFY-EXT [39]	Randomized, double-blinded comparison of two doses of apixaban vs. placebo for extended (>6 mo) therapy in patients with VTE	Apixaban 5 mg BID	334	3 (0.9%)
		Apixaban 2.5 mg BID	353	4 (1.1%)
		Placebo	361	2 (0.6%)
AMPLIFY post-hoc analysis [86]	Post-hoc analysis of bleeding on AMPLIFY	Apixaban	2676	28 (2.5%)
		Enoxaparin/ Warfarin	2689	24 (2.1%)
EINSTEIN CHOICE [40]	Randomized, double-blinded comparison of 2 doses of rivaroxaban vs. aspirin for extended (>6 mo) therapy in patients with VTE	Rivaroxaban 20 mg daily	505	6 (1.2%)
		Rivaroxaban 10 mg daily	507	4 (0.8%)
		Aspirin 100 mg daily	488	1 (0.2%)
EINSTEIN DVT and PE [85] post-hoc analysis	Safety and efficacy of 3-, 6- or 12- month courses of rivaroxaban vs subcutaneous enoxaparin loverlapping with and followed by VKA in patients with acute symptomatic DVT, PE or both	Rivaroxaban 30 mg daily or 20 mg daily	925	19
		Enoxaparin/ VKA	963	3
RE-COVER and RE-MEDY trials Post-hoc analysis [87]	Dabigatran vs. warfarin in the treatment of acute VTE	Dabigatran	643	30 (4.7%)
		Warfarin	637	57 (8.9%)
Hokusai-VTE post-hoc analysis [88]	Edoxaban or warfarin for VTE in reproductive aged women	Edoxaban	628	8 (1.3%)
		Warfarin	665	3 (0.9%)
Standard Therapy 3–6 months				
SELECT-D [41]	Randomized, open-label pilot in patients with cancer and VTE	Rivaroxaban 20 mg daily	87	1 (1.1%)
		Dalteparin 150 IU/kg/d	105	0 (0%)
Caravaggio [42]	Randomized, open-label, non-inferiority trial in patients with cancer and VTE	Apixaban 5 mg BID	284	4 (1.4%)
		Dalteparin 150 IU/kg/d	303	3 (1.0%)
Schastlivtsev et al. [43]	Single-center prospective observational study on patients with upper extremity DVT	Rivaroxaban 20 mg daily	17	1 (5.9%)
Rusin et al. [44]	Single-center prospective case series on patients with CSVT treated with DOAC	Dabigatran 150 mg BID	18	0 (0%)
		Rivaroxaban 20 mg daily	10	2 (20%)
		Apixaban 5 mg BID	8	0 (0%)
Christen et al. [45]	Prospective cohort study of patients with sickle cell disease undergoing VTE treatment with DOACs	Rivaroxaban 20 mg daily	8	4 (50%)

individuals on AC (Table 2). Quantification of bleeding in original AC trials includes uterine MB or CRNMB [37,38]. In Table 2 below, data from relevant AC clinical trials in VTE demonstrate rates of CRNMB.

There were no reported uterine MB events in the 10 studies listed in Table 2, and rates of CRNMB were low. However, reported rates of menorrhagia or intermenstrual bleeding that did not meet CRNMB criteria ranged up to 50%, particularly in patients on rivaroxaban. These trials therefore support the previously performed retrospective studies. Ongoing prospective clinical trials are attempting to better quantify and elucidate AUB while on AC for VTE (NCT02761044, NCT4477837, NCT03772366). Of note, the TEAM-VTE trial (NCT04748393) was terminated due to low accrual. This international, multi-center observational trial was intended to study the management of VTE in menstruating women.

3. Planning for pregnancy while on anticoagulation

Pregnancy planning is of utmost importance in women of childbearing potential on AC. A thorough assessment with a routine complete blood count and ferritin can be helpful in identifying if women are iron deficient and require iron repletion therapy prior to pregnancy. Additionally, careful attention to anticoagulant selection in the peripartum period is crucial, as OACs, particularly warfarin, have teratogenic potential. As heparins do not cross the placenta or result in fetal anticoagulation, they are deemed the safest in this setting. Generally, low molecular weight heparin (LMWH) is the preferred anticoagulant for most pregnant women due to ease of administration, safety and efficacy. Unfractionated heparin is also acceptable. While there is a lack of evidence of potential teratogenicity with novel OACs, there is a concern of fetal bleeding and intracranial hemorrhage due to the ability of being able to cross the placenta. Therefore, avoidance of OACs including warfarin, dabigatran, apixaban, rivaroxaban and edoxaban during pregnancy are crucial. If a woman is utilizing warfarin prior to pregnancy, utilizing LMWH prior to conception is ideal whenever possible. Women on dabigatran, apixaban, rivaroxaban or edoxaban can plan to switch to LMWH once found to be pregnant or may consider switching prior to attempting conception, depending upon personal preference after discussion of potential risks and benefits. LMWH is dosed based on weight and clearance is effected by renal function, therefore some women may require dosage changes throughout their pregnancy. Much controversy exists over whether anti-Xa levels should be monitored and used to adjust dosage during pregnancy and there are no clear data to support one approach over another.

4. Thromboembolism and anticoagulation during pregnancy

Thromboembolism during pregnancy is a challenging circumstance. Pregnancy potentiates a four to five-fold increase in the risk of thromboembolism with high morbidity and mortality [46,47]. The prevalence of VTE in pregnancy is estimated between 0.5 and 2.0 per 1000 pregnant women and VTE is most likely to be identified in the proximal lower extremities [70]. The greatest risk of VTE occurs in the immediate post-partum period. The greatest risk factor for VTE during pregnancy is a history of thromboembolic disease. Cesarean delivery is an independent risk factor for VTE, with an approximate incidence of 3 cases per 1000; this is a four-fold increase in comparison to vaginal delivery. Cesarean deliveries may also be associated with medical conditions that inherently increase the risk of VTE, such as obesity, autoimmune disease, heart disease, hemoglobinopathies, advanced maternal age, multiple gestations and preeclampsias [48–57].

Physiologically and anatomically, pregnancy is a hypercoagulable state due to increased estrogen, increased venous stasis with decreased venous outflow, compression of the inferior vena cava and pelvic veins by an enlarging uterus and decreased general maternal mobility. Hormonally, estrogen causes a prothrombotic state by increasing procoagulant fibrinogen, and factors VII, VIII, X, Von Willebrand factor,

Table 3
Peri-partum anticoagulation guidelines.

Organization	Surveillance without prophylaxis	Ante-partum + Post-partum Prophylaxis	Post-partum prophylaxis Only	Therapeutic Anticoagulation
American College of Chest Physicians (ACCP) [52]	- Women with a history of >2 miscarriages but no documented thrombophilia or APLA - Women with a history of thrombophilia and a history of pregnancy related complications - History of low-risk thrombophilia* with no history of VTE - History of provoked VTE not due to estrogen	- Known APLS - High-risk thrombophilia** and a family history of first degree relative with VTE (no personal history of VTE) - Moderate to high risk of recurrent VTE, including prior history of estrogen provoking VTE	- History of low-risk thrombophilia* with no history of VTE - History of high-risk thrombophilia** without personal or family history of VTE - Personal history of prior VTE	- Pre-pregnancy continuous AC for recurrent VTE - Acute VTE during pregnancy
American College of Obstetrics and Gynecology (ACOG) [77]	- No history of VTE, no thrombophilia - Single provoked VTE without thrombophilia and without estrogen as provoking factor - Low-risk thrombophilia* without previous VTE - Low-risk thrombophilia* with a first-degree family history of VTE	- History of single unprovoked VTE - Low-risk thrombophilia* with single previous episode of VTE - High-risk thrombophilia** without previous VTE - High-risk thrombophilia** with a single episode of previous VTE or first degree family member with VTE	- High-risk thrombophilia** with a single previous VTE or an affected first degree relative with VTE - VTE during pregnancy - History of unprovoked VTE - Low-risk thrombophilia* with a family history of VTE - Low-risk thrombophilia* with a history of VTE	- Two or more episodes of VTE (regardless of thrombophilia, regardless of long term AC) - VTE during pregnancy
American Society of Hematology (ASH) [54]	- Women with no or only 1 clinical risk factor (excluding thrombophilia) - History of provoked VTE (not hormonal) - Low-risk thrombophilia* - High-risk thrombophilia** without family history of VTE - Low-risk* or antithrombin deficiency heterozygote with or without a family history of thrombophilia	- History of VTE that was unprovoked or associated with a hormonal risk factor - Antithrombin deficiency homozygous with a family history of VTE, or Factor V Leiden homozygous or combined high-risk thrombophilia**, regardless of VTE history	- Family history of VTE with low-risk* or high-risk ** thrombophilia - Combined thrombophilia or high-risk thrombophilia**, protein C or S with a history of VTE	- VTE during pregnancy

*Low-risk thrombophilia: Factor V Leiden heterozygote, prothrombin G20210A mutation heterozygote, protein C or S deficiency, antiphospholipid antibody.
** High-risk thrombophilia: Factor V Leiden homozygosity, prothrombin gene G20210A mutation homozygosity, antithrombin deficiency.
APLA = Antiphospholipid antibody syndrome.

plasminogen activator inhibitors-1 and -2 while decreasing free protein S [58].

The utilization of AC in pregnancy warrants special consideration regarding potential effects on the fetus. Given the inherited thrombotic risks associated with pregnancy, women who require AC during pregnancy will need to continue a safe AC method during pregnancy. As discussed above, the preferred anticoagulants during pregnancy are heparin-related compounds such as unfractionated heparin or LMWH, due to their inability to cross the placental barrier. Physiologic changes during pregnancy, such as increased plasma volume and changes in weight can affect the excretion of heparin products through the kidneys and require dose modification. The American College of Obstetrics and Gynecology (ACOG), American Society of Hematology (ASH) and American College of Chest Physicians (ACCP) offer anticoagulation regimen suggestions during pregnancy and in the peripartum period (see Table 3) [59]. The American College of Chest Physicians recommend utilization of LMWH particularly in pregnancy due to appropriate safety profile, reliable pharmacokinetics and ease of administration [52]. DOACs and warfarin generally do not carry acceptable fetal risk profiles in pregnancy, even in the setting of mechanical heart valves, although maternal risks, which may be greater with LMWH must also be considered. ACOG offers guidance to transition to LMWH in these circumstances [59].

Studies demonstrate that oral direct thrombin inhibitors and anti-Xa inhibitors can cross the placenta or be transferred via breast-feeding and therefore DOACs are not recommended in these settings [53,61–63]. In general, heparins including LMWH and unfractionated heparin are deemed safe in the context of breastfeeding. Although some data suggests that warfarin may be safe, compliance with monitoring and dietary restrictions may be particularly challenging in the post-partum period.

5. Considerations for VTE in post-menopausal women

Post-menopausal women commonly utilize hormone replacement therapy (HRT) in various formulations. HRT is delivered by different mechanisms, such as oral, intramuscular, intravaginally, and percutaneously (transdermal). VTE is a major potential complication from the utilization of HRT, particularly with oral estrogens, which increase VTE risk in a dose-dependent fashion [64]. In the E3N Cohort study, incidence of VTE with transdermal HRT is formulation-dependent; micronized progesterone did not change VTE risk (RR 0.93, 95% CI 0.65–1.33), whereas norpregnane derivatives were associated with increased VTE risk (RR 2.42, 95% CI 1.84–3.18) [65]. However, in a systematic review and meta-analysis, twenty-two various studies were surveyed, and it was found that non-oral HRT was not associated with increased VTE risk in comparison to oral, including both non-oral estrogen therapy and non-oral estrogen-progestin therapy [66]. Importantly, this analysis also identified that women who used combined oral HRT in addition to non-oral HRT had an increased risk of VTE. In general, transdermal HRT is considered to be low-risk for VTE, and risk assessment should consider the formulation of the HRT agent.

6. Conclusion

Reporting of AUB, uterine CRNMB and HMB has been inconsistent in many studies of AC including menstruating individuals. The management of HMB while on AC is also heterogeneous. Given the relatively high incidence of VTE in individuals of childbearing potential, careful consideration of choice of AC, duration of AC, concurrent management of HMB, and pregnancy planning are of utmost importance.

While high quality data on the prevention and management of AUB

in anticoagulated women are lacking, principles for management of AUB in non-anticoagulated populations and for prevention and management of other types of bleeding in anticoagulated patients may be applied. A thorough menstrual history prior to the initiation of anticoagulation and continued vigilance for development of HMB is vital. Discussion of the risk of AUB associated with each potential OAC when initiating therapy in a menstruating patient is essential and either apixaban or dabigatran are preferred over rivaroxaban in menstruating individuals who currently or historically suffer from AUB. Patients without a history of AUB or with a successful, ongoing management strategy for AUB should be advised of the high risk of developing HMB or AUB with rivaroxaban and this should be taken into consideration when selecting an agent. In the context of pregnancy planning, heparins and particularly LMWH are the AC of choice during the peripartum and postpartum periods. As heterogeneity exists in the management of AC in menstruating women, there is an unmet need for research to delineate optimal strategies in management of VTE.

Author contributions

(1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] M.G. Beckman, S.E. Critchley, T.L. Ortel, Venous thromboembolism: a public health concern, Am. J. Prev. Med. 38 (2010) S495–S501, https://doi.org/10.1016/j.amepre.2009.12.017.
[2] ESHRE Capri Workshop Group, Venous thromboembolism in women: a specific reproductive health risk, Hum. Reprod. Update 19 (5) (2013) 471–482.
[3] L.D. Bradley, N.A. Gueye, The medical management of abnormal uterine bleeding in reproductive-aged women, Am. J. Obstet. Gynecol. 214 (1) (2015) 31–44.
[4] R. Godin, V. Tagalakis, Abnormal uterine bleeding in women receiving direct oral anticoagulants for the treatment of venous thromboembolism, Vasc. Pharmacol. 93–95 (2017) 1–5.
[5] P.C. Reid, A. Coker, R. Coltart, Assessment of menstrual blood loss using a pictorial chart: a validation study, BJOG 107 (3) (2000) 320–322.
[6] S. Kaatz, A.C. Spyropoulos, S. Schulman, Subcommittee on Control of Anticoagulation. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH, J. Thromb. Haemostasis 13 (11) (2015) 2119–2126.
[7] Z. Liu, P. Blumenthal, R.W. Dubois, A systematic review evaluating health-related quality of life, work impairment, and health-care costs and utilization in abnormal uterine bleeding, Value Health 10 (3) (2007) 183–194.
[8] G.A. Vilos, V. Tureanu, M. Garcia, B. Abu-Rafea, The levonorgestrel intrauterins sytem is an effective treatment in women with abnormal uterine bleeding and anticoagulant therapy, J. Minim. Invasive Gynecol. 16 (4) (2009) 480–484.
[9] L.F. McCaig, National Hospital Ambulatory Medical Care Survey: 2003 Emergency Department Summary. *Advance Data From Vital and Health Statistics of the National Center for Health 358*, 2005.
[10] A.M. Kaunitz, P. Inki, A. Kubba, L. Sanchez-Ramos, Levonorgestrel releasing intrauterine system and endometrial ablation in heavy menstrual bleeding: systematic review and meta-analysis, Obstet. Gynecol. 113 (5) (2009) 1104–1116.
[11] K.A. Matteson, Menstrual health as a part of preventive health care, Obstet. Gynecol. Clin. N. Am. 46 (3) (2019) 441–453.
[12] A. Lethaby, C. Augood, K. Duckitt, Nonsteroidal anti-inflammatory drugs for heavy menstrual bleeding, Cochrane Database Syst. Rev. (2) (2000) CD000400.
[13] A. Kaunitz, Abnormal uterine bleeding in reproductive-age women, J. Am. Med. Assoc. 321 (21) (2019) 2126–2127, https://doi.org/10.1001/jama.2019.5248.
[14] H.O.D. Critchley, E. Babayev, S.E. Bulun, S. Clark, I. Garcia-Grau, P.K. Gregersen, et al., Menstruation: science and society, Am. J. Obstet. Gynecol. 223 (5) (2020).
[15] J. Abbott, J. Hawe, D. Hunter, R. Garry, A double-blind randomized trial comparing the Cavaterm and the NovaSure endometrial ablation systemt for the treatment of dysfunctional uterine bleeding, Fertil. Steril. 80 (203–8) (2003).
[16] R. Hurskainen, J. Teperi, P. Rissanen, A.M. Aalto, S. Grenman, A. Kivelä, et al., Clinical outcomes and costs with the levonorgestrel-releasing intrauterine system or hysterectomy for treatment of menorrhagia: randomized trial 5-year follow up, J. Am. Med. Assoc. 291 (2004) 1456–1463.
[17] R. Hurskainen, Levonorgestrel-releasing intrauterine system in the treatment of heavy menstrual bleeding, Curr. Opin. Obstet. Gynecol. 16 (2004) 487–490.
[18] B.C. Cooper KG, L. Lawrie, D.E. Parkin, A randomized comparison of microwave endometrial ablation with transcervical resection of teh endometrium; follow up at the minimum of five years, BJOG 112 (2005) 470–475.
[19] K.G. Cooper, A.M. Garratt, A.M. Grant, Two-year follow up of women randomised to medical management or transcervical resection of the endometrium for heavy menstrual loss: clinical and quality of life outcomes, Br. J. Obstet. Gynaecol. 106 (1999) 258–265.
[20] T.S. Karlsson, L.B. Marions, M.G. Edlund, Heavy menstrual bleeding significantly affects quality of life, Acta Obstet. Gynecol. Scand. 93 (1) (2014) 52–57.
[21] D. Gath, A. Day, Hysterectomy and psychiatric disorder: I. Levels of psychiatric morbidity beore and after hysterectomy, Br. J. Psychiatry 140 (1982) 335–342.
[22] A. Coulter, A. Long, J. Kelland, S. O'Meara, M.M. Sculpher, F. Song, et al., Managing menorrhagia, Qual. Health Care 4 (1995) 218–226.
[23] A. Coulter, C. Jenkinson, Quality of life and patient satisfaction following treatment for menorrhagia, Fam. Pract. 11 (1994) 394–401.
[24] M. Kuppermann, R.E. Varner, R.L. Summitt Jr., L.A. Learman, C. Ireland, E. Vittinghoff, et al., Effect of hysterectomy vs medical treatment on health-related quality of life and sexual functioning: the medicine or surgery (Ms) randomized trial, J. Am. Med. Assoc. 291 (2004) 1447–1455.
[25] M. Kuppermann, R.L. Summitt Jr., R.E. Varner, S.G. McNeeley, D. Goodman-Gruen, et al., Total or Supracervical Hysterectomy Research Group, Sexual functioning after total compared with supracervical hysterectomy: a randomized trial, Obstet. Gynecol. 105 (2005) 1309–1318.
[26] M. Shapley, P.R. Croft, An epidemiological survey of symptoms of menstrual loss in the community, Br. J. Gen. Pract. 54 (2004) 359–363.
[27] M.J.K. Shapley, P.R. Croft, Increased vaginal bleeding and psychological distress: a longitudinal study of their relationship in the community, BJOG 110 (2003) 548–554.
[28] B. Wright, M.J. Gannon, M. Greenberg, A. House, T. Rutherford, Psychiatric morbidity following endometrial ablation and its association with genuine menorrhagia, BJOG 110 (2003) 358–363.
[29] R.W. Shaw, L. Evans, M.J. Edwards, Perceptions of women on the impact of menorrhagia on their health using multi-attribute utility assessment, Br. J. Obstet. Gynaecol. 105 (1998) 1155–1159.
[30] B. Samuelson Bannow, Management of heavy menstrual bleeding on anticoagulation, Hematology Am Soc Hematol Educ Program 1 (2020) 533–537.
[31] N.P.K. De Crem, T. Vanassche, et al., Abnormal uterine bleeding in VTE patients treated with rivaroxaban compared to vitamin K antagonists, Thromb. Res. 136 (4) (2015) 749–753.
[32] R.M.V. Godin, V. Tagalakis, Abnormal uterine bleeding in women receiving direct oral anticoagulants for the treatment of venous thromboembolism, Vasc. Pharmacol. 93–95 (2017) 1–5.
[33] S. Schulman, C. Kearon, A.K. Kakkar, S. Schellong, H. Eriksson, D. Baanstra, et al., Extended use of dabigatran, warfarin, or placebo in venous thromboembolism, N. Engl. J. Med. 368 (2013) 709–718.
[34] S.K.C. Schulman, C. Kearon, A.K. Kakkar, P. Mismetti, S. Schellong, H. Eriksson, et al., Dabigatran versus warfarin in the treatment of acute venous thromboembolism, N. Engl. J. Med. 361 (2009) 2342–2352.
[35] S.Z. Goldhaber, H. Eriksson, A. Kakkar, S. Schellong, M. Feuring, M. Fraessdorf, et al., Efficacy of dabigatran versus warfarin in patients with acute venous thromboembolism in teh presence of thrombophilia: findings from RE-COVER, RE-COVER II, and RE-MEDY, Vasc. Med. 21 (6) (2016) 506–514.
[36] A.H.P.M. Bryk, K. Plens, A. Undas, Heavy menstrual bleeding in women treated with rivaroxaban and vitamin K antagonists and teh risk of recurrent venous thromboembolism, Vascular [harmacology 87 (2016) 242–247.
[37] S. Kaatz, A.C. Spyropoulos, S. Schulman, Subcommittee on Control of Anticoagulation. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH, J. Thromb. Haemostasis 13 (11) (2015) 2119–2126.
[38] F. Rodeghiero, A. Tosetto, T. Abshire, D.M. Arnold, B. Coller, P. James, et al., ISTH/SCC bleeding assessment tool: a standardized questionnaire and a proposal for a new bleeding score for inherited bleeding disorders, J. Thromb. Haemostasis 8 (9) (2010) 2063–2065.
[39] G. Agnelli, H. Buller, A. Cohen, et al., AMPLIFY-EXT Investigators, Apixaban for extended treatment of venous thromboembolism, N. Engl. J. Med. 368 (8) (2013) 699–708.
[40] J.I. Weitz, A.W.A. Lensing, M.H. Prins, et al., EINSTEIN CHOICE Investigators, Rivaroxaban or aspirin for extended treatment of venous thromboembolism, N. Engl. J. Med. 376 (13) (2017) 1211–1222.
[41] A.M. Young, A. Marshall, J. Thirlwall, O. Chapman, A. Lokare, C. Hill, et al., Comparison of an oral factor Xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: results of a randomized trial (SELECT-D), N. Engl. J. Med. 382 (17) (2018) 1599–1607.

[42] G. Agnelli, C. Becattini, G. Meyer, et al., Caravaggio investigators, Apixaban for the treatment of venous thromboembolism in cancer, N. Engl. J. Med. 382 (2020) 1599–1607.
[43] I. Schastlivtsev, K. Lobastov, S. Tsaplin, I. Kanzafarova, V. Barinov, L. Laberko, et al., Rivaroxaban in the treatment of upper extremity deep vein thrombosis: a single-center experience and review of the literature, Thromb. Res. 181 (2019) 24–28.
[44] G. Rusin, E. Papuga-Szela, J. Żuk, A. Undas, Direct oral anticoagulants in the treatment of cerebral venous sinus thrombosis: a single institution's experience, Neurol. Neurochir. Pol. 53 (5) (2019) 385–387.
[45] J.R. Christen, J. Bertolino, E. Jean, L. Camoin, M. Ebbo, J.R. Harlé, et al., Use of direct oral anticoagulants in patients with sickle cell disease and venous thromboembolism: a prospective cohort study of 12 patients, Hemoglobin 43 (4–5) (2019) 296–299.
[46] J.A. Heit, C.E. Kobbervig, A.H. James, T.M. Petterson, K.R. Bailey, L.J. Melton 3rd, et al., Trends in the incidence of venous thromboembolism during pregnancy or postpartum: a 30-year population-based study, Ann. Intern. Med. 143 (2005) 697–706.
[47] E.R. Pomp, F.R. Rosendaal, C.J. Doggen, Pregnancy, the postpartum period and prothrombotic defects: risk of venous thrombosis in the MEGA study, J. Thromb. Haemostasis 6 (2008) 632–637.
[48] D.R. Danilenko-Dixon, J.A. Heit, M.D. Silverstein, B.P. Yawn, T.M. Petterson, C. M. Lohse, et al., Risk factors for deep vein thrombosis and pulmonary embolism during pregnancy or post partum: a population-based, case-control study, Am. J. Obstet. Gynecol. 184 (2001) 104–110.
[49] T.B. Larsen, M. Gislum, S.P. Johnsen, Maternal smoking, obesity, and risk of venous thromboembolism during pregnancy and the puerperium: a population-based nested case-control study, Thromb. Res. 120 (2007) 505–509.
[50] A.H. James, L.R. Brancazio, E.R. Myers, Venous thromboembolism during pregnancy and the postpartum period: incidence, risk factors, and mortality, Am. J. Obstet. Gynecol. 194 (2006) 1311–1315.
[51] A.H. James, S.Z. Goldhaber, Thrombosis during pregnancy and the postpartum period, Am. J. Obstet. Gynecol. 192 (2005) 216–219.
[52] S.M. Bates, I.A. Greer, S. Middeldorp, D.L. Veenstra, A.M. Prabulos, P.O. Vandvik, VTE, thrombophilia, antithrombotic therapy, and pregnancy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines, Chest 141 (2012) e619S–736S.
[53] S.M. Bates, M. Rodger, A.H. James, I. Greer, Guidance for the treatment and prevention of obstetric-associated venous thromboembolism, J. Thromb. Thrombolysis 41 (2016) 92–128.
[54] S.M. Bates, A.A. Rajasekhar, S. Middeldorp, C. McLintock, M.A. Rodger, A. H. James, et al., American Society of Hematology 2018 guidelines for management of venous thromboembolism: venous thromboembolism in the context of pregnancy, Blood advances 2 (22) (2018) 3317–3359.
[55] Y. Suematsu, Y. Obi, A. Shimomura, R.F. Alizadeh, N.D. Vaziri, N.T. Nguyen, et al., Risk of postoperative venous thromboembolism among pregnant women, Am. J. Cardiol. 120 (2017) 479–483.
[56] P. Lindqvist, K. Marsal, Thrombotic risk during pregnancy: a population study, Obstet. Gynecol. 94 (1999) 595–599.
[57] A.F. Jacobsen, P.M. Sandset, Incidence and risk patterns of venous thromboembolism in pregnancy and puerperium- a register-based case-control study, Am. J. Obstet. Gynecol. 198 (233) (2008) e1–7.
[58] K.A. Bremme, Haemostatic changes in pregnancy, Best Pract. Res. Clin. Haematol. 16 (2) (2003) 153–168.
[59] Committee on Gynecologic Practice, Management of acute abnormal uterine bleeding in nonpregnant reproductive-aged women, Committee Opinion 557 (2013).
[61] P. Bapat, R. Kedar, A. Lubetsky, J.N. Matlow, K. Aleksa, H. Berger, et al., Transfer of dabigatran and dabigatran etexilate mesylate acrosst the dually perfused human placenta, Obstet. Gynecol. 123 (2014) 1256–1261.
[62] P. Bapat, L.S. Pinto, A. Lubetsky, H. Berger, G. Koren, Rivaroxaban transfer acrosst the dually perfused isolated human placental cotyledon, Am. J. Obstet. Gynecol. 213 (710) (2015) e1–6.
[63] P. Bapat, L.S. Pinto, A. Lubetsky, K. Aleksa, H. Berger, G. Koren, Examining the transplacental passage of apixaban using the dually perfused human placenta, J. Thromb. Haemostasis 14 (2016) 1436–1441.
[64] P.Y. Scarabin, Progestogens and venous thromboembolism in menopausal women: an updated oral versus transdermal estrogen meta-analysis, Climacteric 21 (4) (2018) 341–345.
[65] M. Canonico, A. Fournier, L. Carcaillon, V. Olié, G. Plu-Bureau, E. Oger, et al., Postmenopausal hormone therapy and the risk of idiopathic venous thromboembolism: results from the E3N cohort study, Arterioscler. Thromb. Vasc. Biol. 30 (2010) 340–345.
[66] D. Rovinski, R.B. Ramos, T.M. Fighera, G.K. Casanova, P.M. Spritzer, et al., Risk of venous thromboembolism events in postmenopausal women using oral versus non-oral hormone therapy: a systematic review and meta-analysis, Thromb. Res. 168 (2018) 83–95.
[67] D. Aziz, L. Skeith, M.A. Rodger, E. Sabri, M. Righini, M.J. Kovacs, et al., Long-term risk of recurrent venous thromboembolism after a first contraceptive-related event: data from REVERSE cohort study, J. Thromb. Haemostasis 19 (6) (2021) 1526–1532.
[70] W.S. Chan, J.S. Ginsberg, Anatomic distribution of deep vein thrombosis in pregnancy, CMAJ (Can. Med. Assoc. J.) 182 (2010) 657–660.
[77] American College of Obstetrics and Gynecologists, ACOG practice bulletin No. 196: thromboembolism in pregnancy, Obstet. Gynecol. 132 (2018) e1–17.
[84] M.S. Zakherah, S.A. El-Nashar, M.M. Shaaban, Pictorial blood loss assessment chart in the evaluation of heavy menstrual bleeding: diagnostic accuracy compared to alkaline hematin, Gynecol. Obstet. Invest. 71 (4) (2011) 281–284.
[85] I. Martinelli, A. Lensing, S. Middeldorp, M. Levi, J. Beyer-Westendorf, B. van Bellen, et al., Recurrent venous thromboembolism and abnormal uterine bleeding with anticoagulant and hormonal therapy use, Blood 127 (11) (2016) 1417–1425.
[86] M.P. Brekelmans, L.J.J. Scheres, S.M. Bleker, B.A. Hutten, A. Timmermans, H. R. Büller, et al., Abnormal vaginal bleeding in women with venous thromboembolism treated with apixaban or warfarin, Thromb. Haemostasis 117 (4) (2017) 809–815.
[87] M.V. Huisman, M. Ferreira, M. Feuring, M. Fraessdorf, F.A. Klok, Less abnormal uterine bleeding with dabigatran than warfarin in women treated for acute, venous thromboembolism 16 (9) (2018) 1775–1778.
[88] Ljj Scheres, M.P. Brekelmans, W. Ageno, C. Ay, H.R. Büller, S. Eichinger, et al., Abnormal vaginal bleeding in women of reproductive age treated with edoxaban or warfarin for venous thromboembolism: a post hoc analysis of the, Hokusai-VTE study 125 (12) (2018) 1581–1589.