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Reproductive issues in women on direct oral anticoagulants

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Abstract

Direct oral anticoagulants (DOACs) are replacing warfarin and other vitamin K antagonists for a wide range of indications. Advantages of DOAC therapy are fewer food and drug interactions and fixed dosing without routine laboratory monitoring, making DOACs the perfect choice especially for younger patients, in whom the main indication for anticoagulation is prevention and treatment of venous thromboembolism (VTE). Although DOACs are safer and much more convenient than other anticoagulant alternatives, their profile may have drawbacks, especially for younger female patients in whom reproductive issues need special considerations. These may include the issue of heavy menstrual bleeding (HMB) during anticoagulant therapy, the embryotoxicity risk from inadvertent DOAC exposure during pregnancy, and the prevention or planning of pregnancies during DOAC therapy. This review summarizes the most relevant evidence in this increasingly important field of women's health.

KEYWORDS
direct oral anticoagulants, DOAC, embryotoxicity, heavy menstrual bleeding, HMB, pregnancy

Essentials

- Direct oral anticoagulants (DOACs) are the preferred anticoagulants today.
- In women of reproductive age, DOACs may increase the risk of menstrual bleeding.
- Planning of pregnancy and inadvertent DOAC exposure in unplanned pregnancies are additional issues.
- This review provides an overview on the current evidence and clinical guidance for these topics.

1 | INTRODUCTION

Direct oral anticoagulants (DOACs) have replaced warfarin and other vitamin K antagonists (VKAs) for a wide range of indications. Advantages of DOAC therapy are fewer food and drug interactions and fixed dosing without routine laboratory monitoring, making DOACs the perfect choice, especially for younger patients, in whom the main indication for anticoagulation is prevention and treatment of venous thromboembolism (VTE).

Although DOACs are safer and much more convenient than other anticoagulant alternatives, their profile may have drawbacks, especially for younger female patients in whom reproductive issues need special considerations. These may include the risk of heavy menstrual bleeding (HMB) during anticoagulant therapy, the embryotoxicity risk from inadvertent DOAC exposure during pregnancy, and the prevention or planning of pregnancies during DOAC therapy. This review summarizes the most relevant evidence in this increasingly important field of women's health.

2 | HEAVY MENSTRUAL BLEEDING

Heavy menstrual bleeding (HMB) or, according to the International Federation of Gynecology and Obstetrics definition,[1] abnormal uterine bleeding describes increased volume of menstrual blood loss, regardless of regularity, frequency, or duration of the menstrual bleeding. Objectively, HMB is defined as menstrual blood loss of >80 mL with a marked reduction in hemoglobin and plasma iron concentration.[2] A simple clinical tool, the pictorial blood assessment chart (PBAC), validated by Higham et al[3] can help to assess the menstrual blood loss and pattern of menstrual cycle, with a score >100 signifying HMB.[4] In addition to these objective criteria, the subjective patient's perspective and the impact of increased menstrual intensity on overall quality of life should also be taken into consideration.[5] The UK National Institute for Health and Care Excellence defined HMB as excessive menstrual blood loss, which interferes with the woman's physical, emotional, social, and material quality of life.[6]

Increase of HMB by up to 50% has been reported for VKAs, compared to women without anticoagulation.[7-9] Despite the fact that DOACs carry a lower bleeding risk than VKAs, a number of case reports and small case series published soon after the approval of DOACs for VTE treatment raised the concern that DOACs may cause more frequent and more pronounced HMB, though objective comparisons were not provided.[10-12] Unfortunately, all major phase III DOAC trials failed to prespecify prospective analyses on the impact of DOACs on HMB (in comparison with VKA for acute treatment and in comparison with placebo or aspirin in long-term extension treatment), but with increasing real-world reports of HMB during DOAC therapy, post hoc analyses were performed for apixaban, edoxaban, rivaroxaban, and dabigatran VTE treatment trials.

In the AMPLIFY VTE treatment study, HMB was not more frequent with apixaban compared to VKA treatment but menstrual duration tended to be prolonged (odds ratio [OR], 2.3; 95% confidence interval [CI], 0.5-11), and within all bleeds, the proportion of vaginal bleeding was increased (OR, 3.4; 95% CI, 1.8-6.7) compared to the bleeding pattern with VKAs.[13] In the HOKUSAI study, vaginal bleeding was observed in 9% of patients in the edoxaban group compared with 7.1% of patients treated with enoxaparin/warfarin, which translated into a hazard ratio (HR) for abnormal uterine bleeding of 1.7 (95% CI, 1.1-2.5).[14] In the EINSTEIN DVT (deep vein thrombosis) and PE (pulmonary embolism) studies, rivaroxaban was associated with an increased HMB rate compared to enoxaparin/VKA with a HR of 2.13 (95% CI, 1.57-2.89).[15] Obviously, the impact of these three activated factor X (FXa) inhibitors on menstrual blood loss seems to be a class effect. In contrast, in the dabigatran VTE treatment trials (RECOVER I and II), rates of abnormal uterine bleeding were 5.9% in the dabigatran group and 9.6% in the warfarin group, leading to an OR of 0.59 (95% CI, 0.39-0.90), differentiating dabigatran from the other DOACs.[16] An overall DOAC effect on sex-related bleeding patterns was also suggested by a systemic review and meta-analysis of 8 DOAC randomized controlled trials including about 9400 patients with VTE on dabigatran, apixaban, or rivaroxaban versus warfarin. This analysis demonstrated that women suffer more bleeding complications than men when receiving DOACs, and it seems reasonable to conclude that this was mainly driven by HMB events.[17]

A number of clinically relevant questions derive from the observed increase of HMB risk from DOAC therapies:

- What are the underlying mechanisms for this specific bleeding pattern, what are patient-related risk factors, and how will HMB develop over time?
- Which options are available to prevent or treat HMB in younger female DOAC recipients?

With regard to underlying mechanisms and risk profiles, a number of hypotheses have been discussed in the literature. Although a reporting bias in disfavor of a newly approved drug always needs to be considered, it seems unlikely that the described observations are not factual, especially since real-world observations were consistent with the post hoc analyses of several randomized double-blind DOAC trials.

One reasonable explanation is the common practice to stop oral contraception or hormone replacement therapies immediately after a VTE is newly diagnosed, a strategy based on the concern that estrogen is an established risk factor for VTE. If the initiation of anticoagulant therapy (which may generally increase menstrual blood loss) coincides with an abrupt change in hormonal status from hormone withdrawal (a situation that can heavily affect menstrual patterns also in the absence of anticoagulation), this may acutely exacerbate the situation for the patient. Although the hypothesis of hormone withdrawal is very likely an important aspect, this would equally affect patients treated with a VKA or dabigatran. Therefore, this does not explain the specific increase of HMB observed for FXa inhibitors, but a direct impact on coagulation factors or other target proteins in the uterine wall is a reasonable explanation. For instance, FXa inhibitors may exert a synergism with physiological anticoagulants necessary for shedding blood and endometrium cells during menstrual bleeding.[13] Another hypothesis relates to a modulated fibrinolytic function of FXa, which is sequentially cleaved by plasmin. Covalent modification of the FXaα active site inhibits cleavage from FXaα to Xa33/13 by plasmin, leading to increased FXaβ levels. As recently demonstrated by Carter et al,[18] plasma of patients taking rivaroxaban showed enhanced fibrinolytic capacity, which correlated to increased FXaβ levels.

Patient-related risk factors may also contribute to exacerbation of HMB episodes, and such anatomic lesions may be especially susceptible to DOAC-related bleeding. In a case series of 178 women of reproductive age treated with direct oral FXa inhibitors in the noninterventional DRESDEN NOAC REGISTRY, we found that 57 patients reported a total of 72 vaginal bleeding complications—59 cases of HMB and 13 bleedings unrelated to cycle.[19] Most of the vaginal bleeding episodes (54.2%) were minor according to the ISTH definition, 37.5% were clinically relevant nonmajor bleeding, and 8.3% were major bleeding. Twenty-three percent of the 57 women had a second bleeding event, and 4% experienced a third event. Interestingly, underlying anatomic abnormalities (endometriosis,

myoma) were found in 9 women. Compared with patients without such anatomic abnormalities, these patients presented with more intense index bleeding and more (and increasingly severe) recurrent bleeding, necessitating surgical treatments more frequently. We concluded that underlying anatomic abnormalities may predispose patients on FXa inhibitor therapy for HMB, and this effect may well be less pronounced in other anticoagulation strategies. Further research is needed to better understand the pathophysiological background of these observations. The ongoing randomized RAMBLE trial[20] will compare HMB rates during apixaban or rivaroxaban treatment of acute VTE. It is hoped that this study will shed more light on the impact of different FXa inhibitors on menstrual blood loss, although a trial cohort of only 50 patients will likely be underpowered to demonstrate significant differences.

Regarding prevention and treatment of HMB in DOAC patients, a number of clinical strategies can be derived from the literature. First, taking a detailed bleeding history before DOAC prescription is necessary since patients with underlying hemorrhagic conditions such as von Willebrand disease often report suspicious bleeding complications after small surgical procedures or minor trauma. These patients may also describe past episodes of abnormal menstrual bleeding patterns that would predispose them to HMB complications during DOAC therapy. Taking a detailed bleeding history before initiating anticoagulation should generally be good clinical practice, but because of the aforementioned specifics, it should specifically address menstrual bleeding patterns and a dedicated instruction of "what to do in case of menorrhagia" should be part of patient counseling. Based on the potentially different effects of direct FXa inhibitors and dabigatran, the latter may be preferred in patients with suggestive menstrual bleeding history.

Once the indication for anticoagulation is established, physicians should consider continuation of already established hormonal contraception or should even consider commencement of hormonal contraception in women of fertile age. Not only will this strategy reduce the risk for HMB by preventing hormone withdrawal, but it will also help to prevent unintended pregnancies in a patient with acute VTE. A dedicated ISTH guidance recommends against a simultaneous introduction of anticoagulation and discontinuation of hormonal contraception, also because the prothrombotic effect of hormonal therapy is likely to be suppressed by therapeutic-intensity anticoagulation.[21] Post hoc analyses from the EINSTEIN program support this strategy by demonstrating similar VTE rates in patients with and without estrogen exposure during effective anticoagulation.[15]

For treatment of HMB during DOAC therapy, a number of options are available. The most common intervention would be to start systemic hormone treatment, either with progestogen-only contraceptives (POCs) or with combined oral contraceptives (COCs). The first option should generally be preferred since POCs (with the exception of depot medroxyprogesterone acetate [DMPA]) do not increase the risk for VTE, making it possible to continue POCs also once anticoagulation is terminated. If POCs are not accepted or not tolerated by the patient, COCs may be considered. COCs inhibit ovulation and endometrial proliferation, thereby reducing menstrual blood loss.[22-24] COCs also improve menstrual cycle irregularities and symptoms of dysmenorrhea.[25-27] If COCs are considered in DOAC-treated patients with VTE, a preference for second-generation COCs containing ≤35 μg ethinylestradiol combined with a lower-risk progestogen (levonorgestrel, norethisterone, or norgestimate) is recommended.[28,29] However, even these COCs should be stopped when anticoagulation is terminated. Of note, transdermal patches and transdermal etongestrel birth control implants also carry a considerable VTE risk and should be avoided in patients with VTE risk, although they are believed to be effective HMB treatments.[30] DMPA has been shown to be effective in treating HMB,[3,31] but, similar to COCs, DMPA increases the risk for VTE, so it should not be continued once anticoagulation has been stopped.

If oral hormone treatment is not feasible or insufficient to control HMB, the levonorgestrel-releasing intrauterine system (LNG-IUS) is the most effective medical intervention in this setting, reducing the frequency of HMB and surgical treatments by at least 50%.[32-34] Especially in the presence of adenomyosis, uterine fibroids and endometriosis, the LNG-IUS reduces menstrual blood loss and pain associated with these conditions.[35] Levonorgestrel also reduces the endometrial proliferation, resulting in endometrial suppression. The systemic absorption of levonorgestrel is minimal, so systemic progestogenic side effects seem to be rare.

Another pharmacologic approach to treat HMB in DOAC recipients is tranexamic acid (TXA). TXA has proven efficacy in reducing the severity of HMB possibly by improving clot stability in the uterine mucosa by reversibly binding circulating and fibrin-bound plasminogen to inhibit fibrinolysis.[36]

The ongoing MEDEA trial[37] aims to randomize 120 patients experiencing HMB from direct FXa inhibitors into three treatment arms: (i) switch to dabigatran; (ii) continue FXa inhibitor with addition of TXA during the menstrual period; or (iii) continue FXa inhibitor without intervention. The primary outcome will be the difference in the PBAC score before and after randomization.

If HMB is associated with the anticoagulant therapy, dose reduction of DOACs is a natural and reasonable consideration but not acceptable during the first 3 months of VTE treatment, when the risk of acute thromboembolic complications is high and requires the full therapeutic dosage. In this period, switching to out low-molecular-weight heparin (LMWH) or dabigatran is the only option, if all other strategies mentioned above are not feasible or effective. Beyond 3 months from the index VTE, a dose reduction of apixaban and rivaroxaban down to prophylactic dosages (apixaban 2.5 mg twice daily or rivaroxaban 10 mg once daily) may be considered if long-term secondary prevention is indicated, but therapeutic dosages are no longer required. It seems reasonable to expect an improvement of DOAC-related excess menstrual blood loss if DOAC dosages are minimized, but, at present, evidence for such an approach is scarce. Furthermore, DOAC dose reduction may not be possible in all patients, including those with severe thrombophilia.

Finally, surgical or interventional treatment of underlying structural or functional abnormalities in the uterus predisposing for HMB may be indicated in severe cases of HMB.

3 | PREVENTING OR PLANNING PREGNANCIES DURING DOAC THERAPY AND THE RISK OF DOAC EXPOSURE IN PREGNANCY

As stated above, female patients of fertile age with VTE should apply effective measures to prevent unintended pregnancies, especially in the acute phase of disease. Patients at low risk for VTE recurrence intending to become pregnant should complete their DOAC treatment period first, and should then stop contraception and DOAC therapy and aim for pregnancy, during which VTE prevention with LMWH is the established, safe, and effective strategy, if antepartum prophylaxis is indicated.

For patients at higher risk for VTE recurrence, continued preventive measures are indicated, but some patients may be willing to accept reduced efficacy if they can stop DOACs without switching to alternatives. In this situation, a switch to aspirin can be considered, since aspirin has demonstrated some reduction of VTE recurrence in long-term VTE treatment trials.[38,39] However, aspirin use in early pregnancy also carries some bleeding and embryotoxicity risk, and cautious use under close surveillance is recommended.[40]

In patients at high risk for VTE recurrence, anticoagulant treatment may be indicated for unlimited periods of time, during which women may present with a wish to become pregnant. This creates a relevant challenge: Anticoagulation is indicated (and even more so during the prothrombotic state of pregnancy), but the time of conceptional success is unpredictable (and may take years). Therefore, the often practiced concept of "stop DOAC, switch to LMWH before conception, and continue throughout pregnancy" may predispose some patients to long periods of LMWH injection until pregnancy is achieved. Together with the emotional burden of daily injections, also medical side effects need to be discussed: Although generally safe, LMWH is still associated with bleeding complications, allergic reactions, bruising, and, over longer periods of exposure, clinically relevant osteoporosis.

To avoid this burden of long-term preconceptional LMWH, one strategy could be to switch the patient first from a DOAC to a VKA before conception, to continue the VKA until pregnancy is established, and to switch from the VKA to LMWH treatment once pregnancy is confirmed. This concept is currently recommended in guidelines and guidance statements,[41] but the drawbacks are obvious:

- Two switches are necessary (DOAC to VKA and VKA to LMWH).
- Intermittent VKA therapy needs time and frequent monitoring to achieve a stable international normalized ratio (INR).
- Early pregnancy detection and consultation is key to avoid prolonged fetal VKA exposure, which results in higher rates of miscarriages or fatal growth restrictions[42,43] or may cause major birth defect patterns typical for warfarin embryopathy [43-45] in 6%-11% of pregnancies with VKA exposure during weeks 6-12 of gestation.[42,43,46] This time window is critical since many patients present with delayed confirmation of pregnancy and some VKAs (such as phenprocoumon) have very long half-lives, which seems to increase the embryotoxicity risk.[47] As a consequence, VKA exposure often overlaps with the early phase of pregnancy. It is plausible to shorten the VKA "washout" period by vitamin K supplementation, but the evidence for such an approach is weak. Taken together, a switch from a DOAC to a VKA requires acceptance of a considerable embryotoxicity risk and full patient compliance for frequent pregnancy testing and immediate VKA discontinuation once pregnancy is established.
- The question of dosing also needs some consideration. DOACs (at least apixaban and rivaroxaban) and LMWH can be given in low (ie, prophylactic) dosages to prevent recurrent VTE, whereas VKA therapy always requires therapeutic treatment with target INR >2 to achieve sufficient VTE prevention. This strategy would therefore lead to an unnecessarily intense anticoagulation if the patient were to be switched from apixaban 2.5 mg twice daily or rivaroxaban 10 mg once daily (being commonly used prophylactic dosages for VTE secondary prevention) to a VKA with a target INR >2.

Given the complexity of preconceptional switching from a DOAC to LMWH or a VKA, another simple option that needs to be discussed with patients is the continuation of DOACs until pregnancy is confirmed, followed by a direct switch to LMWH. A look into the label of DOACs reveals that DOACs are not strictly contraindicated: there is cautious warning that the use of DOACs in pregnancy is lacking evidence and, therefore, requires careful risk-benefit assessments,[48-51] so DOAC use in pregnancy would not strictly be a "no go." On the other hand, what are the DOAC embryotoxicity data that we can use for a careful risk-benefit assessment?

The placental membrane provides a protective barrier by reducing the entry of drugs into fetal circulation, but small molecules can still cross this barrier.[52] It is estimated that drugs with a molecular weight >500 Dalton (Da) will cross the human placenta in only a small proportion. However, molecular weights of dabigatran, apixaban, and rivaroxaban are <500 Da and edoxaban with 548 Da only slightly higher.[53] Consistent with this, animal and in vitro studies using a human placental perfusion model indicate that apixaban, dabigatran, and rivaroxaban exhibit a relevant placental transfer.[54-56]

In the prescribing information for dabigatran, increased maternal infertility, fetal growth restrictions, and birth defects are described.[48] For apixaban,[49] no signs of fetal harm are listed, but the incidence of maternal bleeding is increased. In the prescribing information for edoxaban, gallbladder anomalies and postimplantation pregnancy loss are reported.[50] For rivaroxaban, postimplantation loss, retarded or progressed ossification, and an increase of common malformations and placental changes are described.[51]

However, so far only few clinical data from case reports and small cohort studies have reported on pregnancy outcomes after

DOAC exposure in pregnancy,[57-59] and many data sources were found to lack important outcome information. This situation was reviewed in a guidance statement from the ISTH in 2016.[60] In this document, the risk of DOAC embryopathy was considered to be sufficiently low to recommend against elective pregnancy termination for fear of DOAC embryotoxicity and in favor of close pregnancy surveillance. However, the authors clearly stated that the available data were insufficient to rule out an embryotoxicity risk from DOAC exposure in pregnancy.

To close this gap in knowledge, an extensive review of documented DOAC exposures in pregnancies was recently performed, summarizing data from the literature, from dedicated registries, from single case reports obtained directly from treating physicians, and from pharmacovigilance systems of drug authorities and DOAC manufacturers.[61] From a total of 1193 reports including duplicates, 614 unique cases could be identified, with information on pregnancy outcome available for 336 cases: 188 live births, 74 miscarriages, and 74 elective pregnancy terminations. In this data set, reported birth anomalies were adjudicated by two independent teratology experts. In a total of 12 of 336 pregnancies (4%; 95% CI, 2%-6%) major birth defects were documented for which a potential association to DOAC exposure could not be ruled out. Furthermore, this reassuringly low number already represented a worst-case scenario and included six cases with insufficient details on DOAC exposure and observed anomalies. When these cases were excluded and only clearly described birth defects were analyzed, the incidence of possible DOAC embryotoxicity was as low as 2% (95% CI, 0%-3%). Of note, observed birth abnormalities after DOAC exposure were very variable and did not follow a distinct pattern, which would be expected from harmful drug exposures in the first or second trimester, as demonstrated for warfarin embryopathy.[46,62]

TABLE 1 Summary of options for counseling DOAC patients intending to become pregnant

Options for women on DOAC therapy planning pregnancy	Pros	Cons
Stop antithrombotic treatment completely before conception	• Easy to explain and simple to execute • Avoids preconceptional burden of parenteral injections • No additional drug intake • No additional bleeding risk • No embryotoxic effects	• No protection from recurrent VTE (suitable only for low-risk patients)
Switch to aspirin before conception	• Easy to explain and simple to execute • Avoids preconceptional burden of parenteral injections	• Less protected from recurrent VTE (compared to LMWH, VKA, or DOAC) • Measurable bleeding risk (compared to no treatment) • Embryotoxic effects in animal models (but seemingly low in humans)
Switch to LMWH before conception	• Protection from recurrent VTE • Variable dosing options • Existing guideline recommendation and established procedure • Requires no further switch after conception • No embryotoxic effects in animal models of humans	• Burdensome parenteral therapy • May require very long preconceptional periods of injections • Risk of osteoporosis from long-term exposure • Measurable bleeding risk (compared to no treatment)
Switch to VKA before and to LMWH after conception (regular pregnancy tests should be conducted, particularly if menstrual periods are irregular, so that a pregnancy can be detected early and an immediate switch made to LMWH)	• Protection from recurrent VTE • Avoids preconceptional burden of parenteral injections • Existing guideline recommendation and established procedure • Oral instead of parenteral	• Difficult to explain and difficult to execute (dietary restrictions; need for INR monitoring; two switching procedures) • Measurable bleeding risk (compared to no treatment) • Considerable embryotoxic effect in animal models and humans • Early pregnancy detection essential
Stay on DOAC and switch to LMWH after conception (regular pregnancy tests should be conducted, particularly if menstrual periods are irregular, so that a pregnancy can be detected early and an immediate switch made to LMWH)	• Protection from recurrent VTE • Easy to explain and simple to execute • Avoids preconceptional burden of parenteral injections • Switch to embryotoxic VKA avoided; resulting in lower risk (based on indirect comparison with VKA data of comparable quality) • Single switch after conception)	• Evidence level less strong compared to LMWH • Lacking guideline recommendations • Measurable bleeding risk (compared to no treatment) • Embryotoxic effects in animal models (but seemingly low in humans) • Early pregnancy detection essential

Abbreviations: DOAC, direct oral anticoagulant; INR, international normalized ratio; LMWH, low-molecular-weight heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism.

These findings are very reassuring. The 2%-4% rate of major birth defects in DOAC-exposed pregnancies is not only lower than the 6% reported for warfarin or the 7%-11% reported for phenprocoumon (of note, the upper 95% CI margin of the worst-case DOAC rate was only 6%), but it also falls into the range of unexposed pregnancies, since anatomic abnormalities occur at a rate of ≈3%.[63,64] Consistent with this, the rate of miscarriages in the DOAC case series was 22%, similar to the risk in the overall population,[65,66] and lower than the 30% miscarriage rate shown for VKA exposure in pregnancy.[42,62]

It can be expected that these recently published data will result in a controversy. Some will correctly point out that data from only 336 evaluable pregnancies are a weak basis to conclude that DOACs can be safely used in female patients planning to conceive. However, given the drawbacks of the alternatives, others will use these reassuring outcome data to at least include the option of "continue DOAC for the time being, test for pregnancy regularly, and switch to LMWH immediately when pregnancy is confirmed" into patient counseling.[67] This approach has also been backed by the GreenTOP guideline 2015.[68] Personally, we have adopted the second, more liberal view but fully accept if other experts in this field remain reluctant until further evidence is available. Since patients and their families will ultimately face the risks and burdens associated with different strategies, they should directly participate in the decision process, for which an open-minded and broad counseling is the basis. Table 1 summarizes the different strategies to provide a basis for such a structured counseling.

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AUTHOR CONTRIBUTIONS

JBW wrote the first draft of the manuscript. SM performed the literature search. Both authors selected the most relevant references, critically revised the manuscript and approved submission.

REFERENCES

1. Munro MG, Critchley HOD, Fraser IS. The FIGO systems for nomenclature and classification of causes of abnormal uterine bleeding in the reproductive years: who needs them? *Am J Obstet Gynecol*. 2012;207(4):259-265.
2. Boonyawat K, O'Brien SH, Bates SM. How I treat heavy menstrual bleeding associated with anticoagulants. *Blood*. 2017;130(24):2603-2609.
3. Higham JM, O'Brien PM, Shaw RW. Assessment of menstrual blood loss using a pictorial chart. *Br J Obstet gynaecology*. 1990;97(8):734-739.
4. Barlow DH, Lumsden MA, Fauser BC, Terrill P, Bestel E. Individualized vaginal bleeding experience of women with uterine fibroids in the PEARL I randomized controlled trial comparing the effects of ulipristal acetate or placebo. *Hum Reprod*. 2014;29(3):480-489.
5. Critchley HO, Munro MG, Broder M, Fraser IS. A five-year international review process concerning terminologies, definitions, and related issues around abnormal uterine bleeding. *Semin Reprod Med*. 2011;29(5):377-382.
6. National Institute for Health Care and Excellence. Heavy menstrual bleeding: assessment and management (NG88). 2018 [Available from: https://www.nice.org.uk/guidance/ng88/resources/heavy-menstrual-bleeding-assessment-and-management-pdf-1837701412549]. Accesssed February 17, 2021.
7. Huq FY, Tvarkova K, Arafa A, Kadir RA. Menstrual problems and contraception in women of reproductive age receiving oral anticoagulation. *Contraception*. 2011;84(2):128-132.
8. Sjalander A, Friberg B, Svensson P, Stigendal L, Lethagen S. Menorrhagia and minor bleeding symptoms in women on oral anticoagulation. *J Thromb Thrombolysis*. 2007;24(1):39-41.
9. van Eijkeren MA, Christiaens GC, Haspels AA, Sixma JJ. Measured menstrual blood loss in women with a bleeding disorder or using oral anticoagulant therapy. *Am J Obstet Gynecol*. 1990;162(5):1261-1263.
10. De Crem N, Peerlinck K, Vanassche T et al. Abnormal uterine bleeding in VTE patients treated with rivaroxaban compared to vitamin K antagonists. *Thromb Res*. 2015;136(4):749-753.
11. Ferreira M, Barsam S, Patel JP et al. Heavy menstrual bleeding on rivaroxaban. *Br J Haematol*. 2016;173(2):314-315.
12. Myers B, Neal R, Myers O, Ruparelia M. Unplanned pregnancy on a direct oral anticoagulant (rivaroxaban): a warning. *Obstet Med*. 2016;9(1):40-42.
13. Brekelmans MP, Scheres LJ, Bleker SM et al. Abnormal vaginal bleeding in women with venous thromboembolism treated with apixaban or warfarin. *Thromb Haemost*. 2017;117(4):809-815.
14. Scheres L, Brekelmans M, Ageno W 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. *BJOG*. 2018;125(12):1581-1589.
15. Martinelli I, Lensing AW, Middeldorp S et al. Recurrent venous thromboembolism and abnormal uterine bleeding with anticoagulant and hormone therapy use. *Blood*. 2016;127(11):1417-1425.
16. Huisman MV, Ferreira M, Feuring M, Fraessdorf M, Klok FA. Less abnormal uterine bleeding with dabigatran than warfarin in women treated for acute venous thromboembolism. *J Thromb Haemost*. 2018;16(9):1775-1778.
17. Alotaibi GS, Almodaimegh H, McMurtry MS, Wu C. Do women bleed more than men when prescribed novel oral anticoagulants for venous thromboembolism? A sex-based meta-analysis. *Thromb Res*. 2013;132(2):185-189.
18. Carter RLR, Talbot K, Hur WS et al. Rivaroxaban and apixaban induce clotting factor Xa fibrinolytic activity. *J Thromb Haemost*. 2018;16(11):2276-2288.
19. Beyer-Westendorf J, Michalski F, Tittl L, Hauswald-Dorschel S, Marten S. Management and outcomes of vaginal bleeding and heavy menstrual bleeding in women of reproductive age on direct oral anti-factor Xa inhibitor therapy: a case series. *Lancet Haematol*. 2016;3(10):e480-e488.
20. Jeffrey Kline Indiana University. RAMBLE - Rivaroxaban vs. Apixaban for Heavy Menstrual Bleeding (RAMBLE): ClinicalTrials.gov; [updated 06 Dec 2019]. Available from: https://clinicaltrials.gov/ct2/show/NCT02829957. Accessed February 17, 2021.
21. Baglin T, Bauer K, Douketis J, Buller H, Srivastava A, Johnson G. Duration of anticoagulant therapy after a first episode of an unprovoked pulmonary embolus or deep vein thrombosis: guidance from the SSC of the ISTH. *J Thromb Haemost*. 2012;10(4):698-702.
22. Coulter A, Kelland J, Peto V, Rees MC. Treating menorrhagia in primary care. An overview of drug trials and a survey of prescribing practice. *Int J Technol Assess Health Care*. 1995;11(3):456-471.
23. Iyer V, Farquhar C, Jepson R. Oral contraceptive pills for heavy menstrual bleeding. *Cochrane Database Syst Rev*. 2000(2):CD000154.

24. Fraser IS, McCarron G. Randomized trial of 2 hormonal and 2 prostaglandin-inhibiting agents in women with a complaint of menorrhagia. *Aust N Z J Obstet Gynaecol*. 1991;31(1):66-70.
25. Grandi G, Barra F, Ferrero S et al. Hormonal contraception in women with endometriosis: a systematic review. *Eur J Contracept Reprod Health Care*. 2019;24(1):61-70.
26. Dragoman MV. The combined oral contraceptive pill – recent developments, risks and benefits. *Best Pract Res Clin Obstet Gynaecol*. 2014;28(6):825-834.
27. Amat L, Bulach A, Leclercq M et al. Additional non-contraceptive effects of contraception: CNGOF Contraception Guidelines. *Gynecol Obstet Fertil Senol*. 2018;46(12):883-888.
28. Dragoman MV, Tepper NK, Fu R, Curtis KM, Chou R, Gaffield ME. A systematic review and meta-analysis of venous thrombosis risk among users of combined oral contraception. *Int J Gynaecol Obstet*. 2018;141(3):287-294.
29. Lidegaard Ø, Løkkegaard E, Svendsen AL, Agger C. Hormonal contraception and risk of venous thromboembolism: national follow-up study. *BMJ*. 2009;339:b2890.
30. Rivara A, James AH. Managing heavy menstrual bleeding in women at risk of thrombosis. *Clin Obstet Gynecol*. 2018;61(2):250-259.
31. Hubacher D, Lopez L, Steiner MJ, Dorflinger L. Menstrual pattern changes from levonorgestrel subdermal implants and DMPA: systematic review and evidence-based comparisons. *Contraception*. 2009;80(2):113-118.
32. Lethaby AE, Cooke I, Rees M. Progesterone/progestogen releasing intrauterine systems versus either placebo or any other medication for heavy menstrual bleeding. *Cochrane Database Syst Rev*. 2000(2):CD002126.
33. Stewart A, Cummins C, Gold L, Jordan R, Phillips W. The effectiveness of the levonorgestrel-releasing intrauterine system in menorrhagia: a systematic review. *BJOG*. 2001;108(1):74-86.
34. Bofill Rodriguez M, Lethaby A, Jordan V. Progestogen-releasing intrauterine systems for heavy menstrual bleeding. *Cochrane Database Syst Rev*. 2020;6:CD002126.
35. Mansour D. Modern management of abnormal uterine bleeding: the levonorgestrel intra-uterine system. *Best Pract Res Clin Obstet Gynaecol*. 2007;21(6):1007-1021.
36. Goshtasebi A, Moukhah S, Gandevani SB. Treatment of heavy menstrual bleeding of endometrial origin: randomized controlled trial of medroxyprogesterone acetate and tranexamic acid. *Arch Gynecol Obstet*. 2013;288(5):1055-1060.
37. Hamulyák EN, Wiegers HMG, Scheres LJJ et al. Heavy menstrual bleeding on direct factor Xa inhibitors: rationale and design of the MEDEA study. *Res Pract Thromb Haemost*. 2020;5(1):223-230.
38. Brighton TA, Eikelboom JW, Mann K et al. Low-dose aspirin for preventing recurrent venous thromboembolism. *N Engl J Med*. 2012;367(21):1979-1987.
39. Becattini C, Agnelli G, Schenone A et al. Aspirin for preventing the recurrence of venous thromboembolism. *N Engl J Med*. 2012;366(21):1959-1967.
40. Intrapharm Laboratories Limited. Aspirin Tablets BP 75 mg Summary of product characteristics. 2020 [updated 30 Mar 2020]. Available from: https://www.medicines.org.uk/emc/product/4172/smpc#gref. Accessed February 17, 2021.
41. Bates SM, Rajasekhar A, Middeldorp S et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: venous thromboembolism in the context of pregnancy. *Blood Adv*. 2018;2(22):3317-3359.
42. Schaefer C, Hannemann D, Meister R et al. Vitamin K antagonists and pregnancy outcome. A multi-centre prospective study. *Thromb Haemost*. 2006;95(6):949-957.
43. van Driel D, Wesseling J, Sauer PJ, Touwen BC, van der Veer E, Heymans HS. Teratogen update: fetal effects after in utero exposure to coumarins overview of cases, follow-up findings, and pathogenesis. *Teratology*. 2002;66(3):127-140.
44. Sathienkijkanchai A, Wasant P. Fetal warfarin syndrome. *J Med Assoc Thai*. 2005;88(suppl 8):S246-S250.
45. Kumar M, Bhasker SK, Singh R, Kohli N, Kumar R. Di Sala syndrome. *BMJ Case Rep*. 2012;2012:bcr1220115291.
46. Walfisch A, Koren G. The, "warfarin window" in pregnancy: the importance of half-life. *J Obstet Gynaecol Can*. 2010;32(10):988-989.
47. Hüttel E, Padberg S, Meister R, Beck E, Schaefer C. Pregnancy outcome of first trimester exposure to the vitamin K antagonist phenprocoumon depends on duration of treatment. *Thromb Haemost*. 2017;117(5):870-879.
48. Boehringer-Ingelheim. Pradaxa 150 mg hard capsules Summary of product characteristics. 2020 [updated 02 Jul 2020]. Available from: http://www.medicines.org.uk/EMC/medicine/24839/SPC/Pradaxa+150. Accessed February 17, 2021.
49. Bristol-Myers Squibb-Pfizer. Eliquis 5 mg film-coated tablets Summary of product characteristics. 2020 [updated 12 Aug 2020]. Available from: https://www.medicines.org.uk/emc/product/2878/smpc. Accessed February 17, 2021.
50. Daiichi Sankyo UK Limited. Lixiana 60mg film-coated tablets summary of product characteristics. 2020 [updated 03 Dec 2020]. Available from: https://www.medicines.org.uk/emc/product/6905/smpc. Accessed February 17, 2021.
51. Bayer Pharma AG. Xarelto 20mg film-coated tablets Summary of product characteristics. 2019 [updated 05 Nov 2019]. Available from: https://www.medicines.org.uk/emc/product/2793/smpc. Accessed February 17, 2021.
52. Ganapathy V, Prasad PD, Ganapathy ME, Leibach FH. Placental transporters relevant to drug distribution across the maternal-fetal interface. *J Pharmacol Exp Ther*. 2000;294(2):413-420.
53. Ieko M, Naitoh S, Yoshida M, Takahashi N. Profiles of direct oral anticoagulants and clinical usage-dosage and dose regimen differences. *J Intens Care*. 2016;4(1):19.
54. Wang L, He K, Maxwell B et al. Tissue distribution and elimination of [14C]apixaban in rats. *Drug Metab Dispos*. 2011;39(2):256-264.
55. Bapat P, Kedar R, Lubetsky A et al. Transfer of dabigatran and dabigatran etexilate mesylate across the dually perfused human placenta. *Obstet Gynecol*. 2014;123(6):1256-1261.
56. Bapat P, Pinto LS, Lubetsky A, Berger H, Koren G. Rivaroxaban transfer across the dually perfused isolated human placental cotyledon. *Am J Obstet Gynecol*. 2015;213(5):710.e1-710.e6.
57. Konigsbrugge O, Langer M, Hayde M, Ay C, Pabinger I. Oral anticoagulation with rivaroxaban during pregnancy: a case report. *Thromb Haemost*. 2014;112(6):1323-1324.
58. Hoeltzenbein M, Beck E, Meixner K, Schaefer C, Kreutz R. Pregnancy outcome after exposure to the novel oral anticoagulant rivaroxaban in women at suspected risk for thromboembolic events: a case series from the German Embryotox Pharmacovigilance Centre. *Clin Res Cardiol*. 2016;105(2):117-126.
59. Beyer-Westendorf J, Michalski F, Tittl L et al. Pregnancy outcome in patients exposed to direct oral anticoagulants - and the challenge of event reporting. *Thromb Haemost*. 2016;116(4):651-658.
60. Cohen H, Arachchillage DR, Middeldorp S, Beyer-Westendorf J, Abdul-Kadir R. Management of direct oral anticoagulants in women of childbearing potential: guidance from the SSC of the ISTH: reply. *J Thromb Haemost*. 2017;15(1):195-197.
61. Beyer-Westendorf J, Tittl L, Bistervels I et al. Safety of direct oral anticoagulant exposure during pregnancy: a retrospective cohort study. *Lancet Haematol*. 2020;7(12):e884-e891.
62. Van Driel D, Wesseling J, Sauer PJJ, Touwen BCL, Van Der Veer E, Heymans HSA. Teratogen update: fetal effects after in utero exposure to coumarins overview of cases, follow-up findings, and pathogenesis. *Teratology*. 2002;66(3):127-140.
63. Hothi DK, Wade AS, Gilbert R, Winyard PJ. Mild fetal renal pelvis dilatation: much ado about nothing? *Clin J Am Soc Nephrol*. 2009;4(1):168-177.

64. Sewell MD, Rosendahl K, Eastwood DM. Developmental dysplasia of the hip. *BMJ*. 2009;339:b4454.
65. Savitz DA, Hertz-Picciotto I, Poole C, Olshan AF. Epidemiologic measures of the course and outcome of pregnancy. *Epidemiol Rev*. 2002;24(2):91-101.
66. Buss L, Tolstrup J, Munk C et al. Spontaneous abortion: a prospective cohort study of younger women from the general population in Denmark. Validation, occurrence and risk determinants. *Acta Obstet Gynecol Scand*. 2006;85(4):467-475.
67. Bauer KA. Use of anticoagulants during pregnancy and postpartum: UpToDate®; 2020 [updated Aug 19, 2020]. Available from: https://www.uptodate.com/contents/use-of-anticoagulants-during-pregnancy-and-postpartum#H9371507. Accessed February 17, 2021.
68. Nelson-Piercy C, MacCallum P, Mackillop L. Royal College of Obstetricians and Gynaecologists. Reducing the Risk of Venous Thromboembolism during Pregnancy and the Puerperium Green-top Guideline No. 37a. 2015 [Available from: https://www.rcog.org.uk/globalassets/documents/guidelines/gtg-37a.pdf]. Accessed February 17, 2021.

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