DOACs and Breastfeeding

1. Direct Oral Anticoagulants and Women

**Author(s):** Cohen H.; Arachchilage D.R.J.; Beyer-Westendorf J.; Middeldorp S.; Kadir R.A.

**Source:** Seminars in Thrombosis and Hemostasis; Oct 2016; vol. 42 (no. 7); p. 789-797

**Publication Date:** Oct 2016

**Publication Type(s):** Article

**PubMedID:** 27706531

**Abstract:** Direct oral anticoagulants (DOACs) provide an effective, safe, and convenient therapeutic alternative to warfarin and other vitamin K antagonists (VKAs), and are now established for a wide range of indications. The use of DOACs in women merits special consideration due to two main situations: first, in relation to fertility, pregnancy, and lactation in women of reproductive age; second, because of their bleeding risk, leading to abnormal uterine and/or other genital tract bleeding. This review focuses on these two clinical situations, including approaches to management in the context of available information.

2. Management of direct oral anticoagulants in women of childbearing potential: guidance from the SSC of the ISTH

**Author(s):** Cohen H.; Arachchilage D.R.; Middeldorp S.; Beyer-Westendorf J.; Abdul-Kadir R.

**Source:** Journal of Thrombosis and Haemostasis; Aug 2016; vol. 14 (no. 8); p. 1673-1676

**Publication Date:** Aug 2016

**Publication Type(s):** Article

**PubMedID:** 27346676

Available at [Journal of Thrombosis and Haemostasis](https://onlinelibrary.wiley.com/doi/10.1111/jth.12964) - from Wiley Online Library Science, Technology and Medicine Collection 2017
3. The Direct Factor Xa Inhibitor Rivaroxaban Passes Into Human Breast Milk.

**Author(s):** Wiesen, Martin H J; Blaich, Cornelia; Müller, Carsten; Streichert, Thomas; Pfister, Roman; Michels, Guido

**Source:** Chest; Jul 2016; vol. 150 (no. 1); p. e1

**Publication Date:** Jul 2016

**Publication Type(s):** Case Reports Journal Article

**PubMedID:** 27396794

Available at [Chest](https) - from Free Medical Journals . com

**Abstract:** Thromboembolic disorders frequently require antithrombotic treatment during pregnancy and lactation. Vitamin K antagonists and heparins are the treatment options of choice in breastfeeding women. Factors including the route of administration, discomfort during treatment, and fetal and neonatal safety affect women's choices about anticoagulant therapy. Direct-acting oral anticoagulants (DOACs) have emerged as alternatives to these agents and may offer advantages compared with vitamin K antagonists. As breastfeeding women were excluded from clinical trials evaluating DOACs, no safety and efficacy data are available for these special patients and, crucially, estimates for infant exposure are lacking. Therefore, the manufacturer recommends against using DOACs during the lactation period. We present the case of a patient who stopped breastfeeding owing to a diagnosis of postpartum cardiomyopathy. Anticoagulation with enoxaparin that commenced after the diagnosis of postpartum pulmonary embolism was switched to rivaroxaban. At that time, breast milk samples were collected and rivaroxaban concentrations were determined by liquid chromatography tandem-mass spectrometry. Rivaroxaban appears in human breast milk in comparatively small amounts; its safety has not been determined.

**Database:** Medline


**Author(s):** Myers, B; Neal, R; Myers, O; Ruparelia, M

**Source:** Obstetric medicine; Mar 2016; vol. 9 (no. 1); p. 40-42

**Publication Date:** Mar 2016

**Publication Type(s):** Journal Article

**PubMedID:** 27512489

Available at [Obstetric Medicine](https) - from Europe PubMed Central - Open Access

**Abstract:** Direct oral anticoagulants (DOACs or NOACs -non-vitamin K oral anticoagulants), as the name suggests, are oral anticoagulants with a direct inhibitory action either against factor X or factor II (thrombin). Pregnant women were excluded from participating in all the large trials of the DOACs and they are considered contra-indicated in pregnancy and breast feeding. We present a case of inadvertent exposure to rivaroxaban in a woman who presented at 25 weeks’ gestation. The management of her pregnancy and delivery is described, and the previous published case reports are reviewed with a discussion about the use of DOACs in woman of childbearing age.

**Database:** Medline
5. A systematic review on the use of new anticoagulants in pregnancy.

Author(s): Tang, Ai-Wei; Greer, Ian

Source: Obstetric medicine; Jun 2013; vol. 6 (no. 2); p. 64-71

Publication Date: Jun 2013

Publication Type(s): Journal Article

PubMedID: 27757159

Available at Obstetric Medicine - from Europe PubMed Central - Open Access

Abstract: New anticoagulants such as direct factor Xa inhibitors and direct thrombin inhibitors have been recently developed, but their experience in pregnancy is limited. This review therefore aims to systematically search for studies on the use of these newer anticoagulants in pregnancy and the puerperal period. Searches were performed on electronic databases MEDLINE (from 1966), EMBASE (from 1974) and the Cochrane Library, until October 2011 using terms of 'pregnancy', 'puerperium', 'breastfeeding' and names of specific anticoagulants. The search yielded 561 citations and 11 studies (10 on fondaparinux, 1 on ximelagatran) were included. Newer anticoagulants (fondaparinux, hirudin and argatroban) on the limited evidence appear not to have adverse pregnancy outcomes, but there is currently no experience of new oral anticoagulants (rivaroxaban, apixaban, betrixaban or dabigatran) use in pregnancy. There is a need for reporting on new oral anticoagulation use in pregnancy to provide more information about the safety and risks to the fetus in utero.

Database: Medline

6. Direct Oral Anticoagulants for Thromboprophylaxis in Patients with Antiphospholipid Syndrome

Author(s): Cohen H.; Efthymiou M.; Gates C.; Isenberg D.

Source: Seminars in Thrombosis and Hemostasis; Jul 2018; vol. 44 (no. 5); p. 427-438

Publication Date: Jul 2018

Publication Type(s): Article

Available at Seminars in thrombosis and hemostasis - from Unpaywall

Abstract: The current mainstay of the treatment and secondary thromboprophylaxis of thrombotic antiphospholipid syndrome (APS) is anticoagulation with warfarin or other vitamin K antagonists (VKAs). In addition to their well-known limitations, VKAs are often problematic in APS patients because of the variable sensitivity of thromboplastins to lupus anticoagulant. As a result, the international normalized ratio may not accurately reflect the intensity of anticoagulation. Direct oral anticoagulants (DOACs) are established as therapeutic alternatives to VKAs for a wide range of indications, including the treatment and secondary prevention of venous thromboembolism. Definition of the role of DOACs in the treatment of thrombotic APS is emerging with the results of recent and ongoing clinical studies. This review focuses on the current situation with regard to DOACs for secondary thromboprophylaxis in APS and issues pertinent to DOAC use in APS patients, as well as potential future directions.

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Database: EMBASE
7. Direct oral anticoagulants: Current indications and unmet needs in the treatment of venous thromboembolism

**Author(s):** Bertoletti L.; Duvillard C.; De Magalhaes E.; Mismetti P.; Ollier E.; Delavenne X.; Beyens M.-N.; Basset T.; Laporte S.; Bellet F.

**Source:** Pharmacological Research; Apr 2017; vol. 118; p. 33-42

**Publication Date:** Apr 2017

**Publication Type(s):** Review

**PMID:** 27350265

**Abstract:** The treatment of acute venous thromboembolism (VTE) is being completely modified with the development of direct oral anticoagulants (DOACs). Rivaroxaban, apixaban and edoxaban directly inhibit factor Xa, whereas dabigatran inhibits factor IIa. All these drugs are proposed orally, and share pharmacological similarities: fixed doses without any therapeutic drug monitoring, key role of the transporter proteins P-glycoprotein for all of them and metabolism mediated by CYP3A4 for the anti-Xa, short half-life with variable rate of renal elimination. More than 25,000 patients with acute VTE were included in phase-III studies. Rivaroxaban and apixaban challenged all the conventional therapy (parenteral heparins followed by anti-vitamin K antagonists) whereas edoxaban and dabigatran challenged only anti-vitamin K antagonists. All the DOACs met the non-inferiority efficacy endpoint (recurrent VTE during treatment), whereas the large non-inferiority margin was debated for dabigatran. However, they were associated with better safety and a decreased risk of major bleeding. According to indirect comparisons, there were no statistically significant differences between DOACs in terms of efficacy but some differences are not excluded in terms of safety. Although DOACs allow for simplification of treatment in the majority of patients with acute VTE, their risk/benefit ratio is questioned in elderly patients, patients with mild-to-severe renal impairment, and in some clinical subgroups such as cancer or chronic thromboembolic pulmonary hypertension. Validated reversal strategies (potentially based on laboratory monitoring) are expected for patients with major bleeding, overdose or with a need for surgery. Copyright © 2016 Elsevier Ltd

**Database:** EMBASE

8. Guidance for the practical management of the direct oral anticoagulants (DOACs) in VTE treatment

**Author(s):** Burnett A.E.; Mahan C.E.; Vazquez S.R.; Oertel L.B.; Garcia D.A.; Ansell J.

**Source:** Journal of Thrombosis and Thrombolysis; Jan 2016; vol. 41 (no. 1); p. 206-232

**Publication Date:** Jan 2016

**Publication Type(s):** Article

**PMID:** 26780747

Available at [Journal of Thrombosis and Thrombolysis](https://www.ncbi.nlm.nih.gov/pubmed/26780747) - from PubMed Central

**Abstract:** Venous thromboembolism (VTE) is a serious medical condition associated with significant morbidity and mortality, and an incidence that is expected to double in the next forty years. The advent of direct oral anticoagulants (DOACs) has catalyzed significant changes in the therapeutic landscape of VTE treatment. As such, it is imperative that clinicians become familiar with and appropriately implement new treatment paradigms. This manuscript, initiated by the Anticoagulation Forum, provides clinical guidance for VTE treatment with the DOACs. When possible, guidance statements are supported by existing published evidence and guidelines. In instances where evidence or guidelines are lacking, guidance statements represent the consensus opinion of all authors of this manuscript and are endorsed by the Board of Directors of the
Anticoagulation Forum. The authors of this manuscript first developed a list of pivotal practical questions related to real-world clinical scenarios involving the use of DOACs for VTE treatment. We then performed a PubMed search for topics and key words including, but not limited to, apixaban, antidote, bridging, cancer, care transitions, dabigatran, direct oral anticoagulant, deep vein thrombosis, edoxaban, interactions, measurement, perioperative, pregnancy, pulmonary embolism, reversal, rivaroxaban, switching, thrombophilia, venous thromboembolism, and warfarin to answer these questions. Non-English publications and publications > 10 years old were excluded. In an effort to provide practical information about the use of DOACs for VTE treatment, answers to each question are provided in the form of guidance statements, with the intent of high utility and applicability for frontline clinicians across a multitude of care settings. Copyright © 2016, The Author(s).

**Database:** EMBASE

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9. Use of new oral anticoagulants in antiphospholipid syndrome.

**Author(s):** Arachchilage, Deepa Jayakody; Cohen, Hannah

**Source:** Current rheumatology reports; Jun 2013; vol. 15 (no. 6); p. 331

**Publication Date:** Jun 2013

**Publication Type(s):** Journal Article Review

**PubMedID:** 23649961

Available at *Current Rheumatology Reports* - from SpringerLink

**Abstract:** The current mainstay of treatment of thrombotic APS is long-term anticoagulation with oral vitamin K antagonists (VKA) such as warfarin. However, the use of warfarin is problematic, particularly in patients with antiphospholipid syndrome (APS). The new oral anticoagulants (NOAC) include dabigatran etexilate (Pradaxa®), a direct thrombin inhibitor, and rivaroxaban (Xarelto®), Apixaban (Eliquis) and Edoxaban (Lixiana®), which are direct anti-Xa inhibitors. Unlike warfarin, these agents do not interact with dietary constituents and alcohol, have few reported drug interactions, and monitoring of their anticoagulant intensity is not routinely required due to their predictable anticoagulant effects. In this chapter, we discuss clinical and laboratory aspects of NOAC. These agents have been approved for several therapeutic indications based on phase III prospective randomised controlled clinical trials using warfarin at a target INR of 2.5 (i.e. range 2.0-3.0) as the comparator. However these trials may not be directly applicable to patients with antiphospholipid syndrome (APS) where prospective clinical studies of NOAC are the way forward.

**Database:** Medline
10. Guidelines for Use of Anticoagulation in Pregnancy

**Author(s):** Fuller K.P.; Turner G.; Polavarapu S.; Prabulos A.-M.

**Source:** Clinics in Laboratory Medicine; Jun 2013; vol. 33 (no. 2); p. 343-356

**Publication Date:** Jun 2013

**Publication Type(s):** Review

**PubMedID:** 23702122

**Abstract:** This article reviews anticoagulant medications used for obstetric patients who have acute thrombosis or who require anticoagulant therapy for other indications. Medication options, dosing and monitoring, side effects, and complications are reviewed. Antepartum, intrapartum, and postpartum management of therapy is discussed, as well as breastfeeding options. © 2013 Elsevier Inc.

**Database:** EMBASE


**Author(s):** Bates S.M.; Greer A.; Middeldorp S.; Veenstra D.L.; Prabulos A.-M.; Vandvik P.O.

**Source:** Chest; Feb 2012; vol. 141 (no. 2)

**Publication Date:** Feb 2012

**Publication Type(s):** Review

**PubMedID:** 22315276

**Abstract:** Background: The use of anticoagulant therapy during pregnancy is challenging because of the potential for both fetal and maternal complications. This guideline focuses on the management of VTE and thrombophilia as well as the use of antithrombotic agents during pregnancy. Methods: The methods of this guideline follow the Methodology for the Development of Antithrombotic Therapy and Prevention of Thrombosis Guidelines: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines in this supplement. Results: We recommend low-molecular-weight heparin for the prevention and treatment of VTE in pregnant women instead of unfractionated heparin (Grade 1B). For pregnant women with acute VTE, we suggest that anticoagulants be continued for at least 6 weeks postpartum (for a minimum duration of therapy of 3 months) compared with shorter durations of treatment (Grade 2C). For women who fulfill the laboratory criteria for antiphospholipid antibody (APLA) syndrome and meet the clinical APLA criteria based on a history of three or more pregnancy losses, we recommend antepartum administration of prophylactic or intermediate-dose unfractionated heparin or prophylactic low-molecular-weight heparin combined with low-dose aspirin (75-100 mg/d) over no treatment (Grade 1B). For women with inherited thrombophilia and a history of pregnancy complications, we suggest not to use antithrombotic prophylaxis (Grade 2C). For women with two or more miscarriages but without APLA or thrombophilia, we recommend against antithrombotic prophylaxis (Grade 1B). Conclusions: Most recommendations in this guideline are based on observational studies and extrapolation from other populations. There is an urgent need for appropriately designed studies in this population. © 2012 American College of Chest Physicians.

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