Rivaroxaban and Lactation

1. Venous thromboembolism and women's health.
   **Author(s):** Speed, Victoria; Roberts, Lara N; Patel, Jignesh P; Arya, Roopen
   **Source:** British journal of haematology; Nov 2018; vol. 183 (no. 3); p. 346-363
   **Publication Date:** Nov 2018
   **Publication Type(s):** Journal Article Review
   **PubMedID:** 30334572
   **Available at** British journal of haematology - from Wiley Online Library Science, Technology and Medicine Collection 2017
   **Abstract:** The prevention and treatment of venous thromboembolism (VTE) poses distinct gender-specific challenges. Women of childbearing age are at an increased risk of VTE secondary to the transient risk factors of combined hormonal contraception (CHC) and pregnancy. Cancers specific to women are associated with a significant burden of VTE; whilst the incidence of VTE in localised breast cancer is 5 per 1000 person-years, more cases are seen due to the prevalence of breast cancer. Treatment of VTE in women can be complicated by abnormal uterine bleeding, now increasingly reported with direct oral anticoagulants (DOACs) as well as vitamin K antagonists. Divergence between international guidelines regarding the use of CHC following an oestrogen-associated VTE and appropriate withdrawal of such contraception requires clarification for clinicians. Additionally, there is uncertainty as to whether to consider such events provoked or unprovoked and, consequently, the optimal duration of treatment in these women remains unclear. During pregnancy and the puerperium, the traditional anticoagulants remain the agents of choice with no further advances in DOAC safety data, and similarly in lactation. Further studies evaluating the safety and optimal treatment strategies in these women are awaited.
   **Database:** Medline
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


**Database:** EMBASE

3. 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](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3708363/) 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
4. The Direct Factor Xa Inhibitor Rivaroxaban Passes Into Human Breast Milk

**Author(s):** Wiesen M.H.J.; Blaich C.; Muller C.; Streichert T.; Pfister R.; Michels G.

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

**Publication Date:** Jul 2016

**Publication Type(s):** Article

**PubMedID:** 27396794

Available at Chest - 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. Copyright © 2016 American College of Chest Physicians

**Database:** EMBASE

5. Unplanned pregnancy on a direct oral anticoagulant (Rivaroxaban): A warning

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

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

**Publication Date:** Mar 2016

**Publication Type(s):** Article

Available at Obstetric medicine - 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. Copyright © 2015, © The Author(s) 2015.

**Database:** EMBASE
6. Antithrombotic therapy for pregnant women

**Author(s):** Toyoda K.

**Source:** Neurologia Medico-Chirurgica; Aug 2013; vol. 53 (no. 8); p. 526-530

**Publication Date:** Aug 2013

**Publication Type(s):** Article

**PubMedID:** 23979047

Available at Neurologia Medico-Chirurgica - from Europe PubMed Central - Open Access

**Abstract:** Coagulability increases during pregnancy, and thromboembolism can easily occur. Venous thromboembolism is a cause of death in pregnant women, but arterial thrombosis such as ischemic stroke in pregnancy is also not uncommon. In pharmacotherapy for thromboembolism in pregnant women, fetal toxicity and teratogenicity must be carefully considered. As anticoagulants in pregnant women, unfractionated heparin and low-molecular-weight heparin are recommended, but warfarin is not recommended since it has a low molecular weight and crosses the placenta. Various types of new oral anticoagulant drugs have been available in Japan since 2011. However, the Japanese package inserts for these anticoagulants advise quite cautious administration in pregnant women. The guidelines on pregnant women include less information about antiplatelet drugs than anticoagulant drugs. Aspirin may cause teratogenicity and fetal toxicity, and perinatal mortality is increased. However, when low doses of aspirin are administered as antiplatelet therapy, the US Food and Drug Administration has assigned pregnancy category C, and treatment is relatively safe. Neurosurgeons and neurologists commonly encounter pregnant women with thromboembolism, such as ischemic stroke. Up-to-date information and correct selection of drugs are necessary in consultation with specialists in perinatal care.

**Database:** EMBASE

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7. 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

Available at Chest - from Free Medical Journals . com

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.

Database: EMBASE
9. Possible rivaroxaban failure during the postpartum period

**Author(s):** Rudd K.M.; Winans A.R.M.; Panneerselvam N.

**Source:** Pharmacotherapy; Nov 2015; vol. 35 (no. 11)

**Publication Date:** Nov 2015

**Publication Type(s):** Article

Available at Pharmacotherapy - from Wiley Online Library Science, Technology and Medicine Collection 2017

**Abstract:** Rivaroxaban, a factor Xa inhibitor, is a direct-acting oral anticoagulant (DOAC) indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and for reducing the risk of DVT and PE recurrence. To our knowledge, no data are presently available to guide DOAC dosing in the postpartum period when pharmacokinetic and pharmacodynamic changes induced by pregnancy have an impact on drug clearance and increase hypercoagulability for a period of 6-8 weeks after delivery. We describe the case of a 35-year-old postpartum woman who presented to the emergency department with a diagnosis of a new multiple segmental PE 5 days after starting rivaroxaban therapy for a diagnosis of DVT. No precipitating cause, including noncompliance, was identified as a source of thrombosis embolization or extension. The patient was admitted, a heparin infusion was started for the management of PE, and rivaroxaban was discontinued. She was transitioned to enoxaparin 1 mg/kg (90 mg) subcutaneously every 12 hours the next day, bridged to warfarin, and discharged home on the overlapping regimen with close follow-up by the pharmacist-managed outpatient Anticoagulation Management Service. To our knowledge, this is the first case report of potential failure associated with rivaroxaban therapy in the postpartum period, possibly due to pharmacokinetic alterations seen in the postpartum period contributing to decreased drug exposure, yielding reduced anticoagulant efficacy. Clinicians should carefully weigh the risks and benefits of DOAC therapy in postpartum patients or other special populations requiring anticoagulation therapy. This report also highlights the need for further research identifying the impact of pharmacokinetic changes induced by special populations and the need to develop monitoring assays for such clinical situations. Copyright © 2015 Pharmacotherapy Publications, Inc.

**Database:** EMBASE


**Author(s):** Naoum, Joseph; Mohsen, Amani; Daher, Jihad; Eid, Toufic

**Source:** Saudi pharmaceutical journal : SPJ : the official publication of the Saudi Pharmaceutical Society; Jul 2018; vol. 26 (no. 5); p. 608-610

**Publication Date:** Jul 2018

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

**PubMedID:** 29988955

Available at Saudi pharmaceutical journal : SPJ : the official publication of the Saudi Pharmaceutical Society - from Europe PubMed Central - Open Access

**Abstract:** Ovarian vein thrombosis (OVT) is a rare serious diagnosis especially if extending to inferior vein cava (IVC). We present a case of 36-year-old female who was diagnosed with right OVT reaching the inferior vein cava following a supra-cervical hysterectomy that was performed in the postpartum period due to excessive bleeding from uterine fibroids. Using the new generation anticoagulant "rivaroxaban" for six months followed by maintenance regimen of aspirin and sulodexide, complete resolution of the clot was noticed without any adverse event while using this regimen. This is the first OVT case which is completely treated with rivaroxaban without any adjunct invasive modality.
11. Prevention of venous thromboembolism in pregnant patients with a history of venous thromboembolic disease: A retrospective cohort study

**Author(s):** Lazo-Langner A.; Al-Ani F.; Weisz S.; Rozanski C.; Louzada M.; Kovacs J.; Kovacs M.J.

**Source:** Thrombosis Research; Jul 2018; vol. 167 ; p. 20-25

**Publication Date:** Jul 2018

**Publication Type(s):** Article

**Abstract:** Background: Optimal prophylactic strategies in pregnant women with a history of venous thromboembolism (VTE) are unknown. Patients and methods: We conducted a retrospective cohort study of consecutive pregnant patients with a previous VTE history. Patients were followed until 6 weeks postpartum. Patients with a previous unprovoked event (including antepartum VTE) received antenatal prophylaxis, mostly with low dose low molecular weight heparin (LMWH). All patients received prophylaxis for six weeks after delivery. Results: We included a total of 199 pregnancies in 142 women. Of these, 147 pregnancies occurred in women with unprovoked or estrogen-related VTE history and 52 pregnancies in women with provoked VTE. There were 8 recurrences in 199 pregnancies (4%; 95%CI: 2.05-7.73), of which 5 were antepartum recurrences (2.5%; 95%CI 1.08-5.75) and 3 were postpartum (1.5%; 95% CI 0.51-4.34). In the unprovoked VTE group there were 7 recurrences (4.7%; 95%CI: 2.32-9.50), whereas in the provoked VTE group there was 1 (1.9%; 95%CI: 0.34-10.12). There was one major bleeding event in a patient not receiving LMWH secondary to placental abruption. Conclusion: This study suggests that the use of prophylactic doses of LMWH during pregnancy and puerperium, as described in this study, results in low occurrence of ante- and postpartum VTE recurrences in patients with previous VTE. Further studies are required to confirm this observation.

Database: EMBASE


**Author(s):** Königsbrügge, O; Langer, M; Hayde, M; Ay, C; Pabinger, I

**Source:** Thrombosis and haemostasis; Dec 2014; vol. 112 (no. 6); p. 1323-1324

**Publication Date:** Dec 2014

**Publication Type(s):** Letter Case Reports

**PubMedID:** 25055834

Database: Medline
13. 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.

Author(s): Hoeltzenbein, M; Beck, E; Meixner, K; Schaefer, C; Kreutz, R

Source: Clinical research in cardiology : official journal of the German Cardiac Society; Feb 2016; vol. 105 (no. 2); p. 117-126

Publication Date: Feb 2016

Publication Type(s): Journal Article

PubMedID: 26195125

Available at Clinical research in cardiology : official journal of the German Cardiac Society - from ProQuest (Hospital Premium Collection) - NHS Version

Available at Clinical research in cardiology : official journal of the German Cardiac Society - from SpringerLink

Abstract: BACKGROUND New oral anticoagulants are increasingly used in women of childbearing age, but apart from one case report there is no published experience with rivaroxaban exposure during pregnancy. METHODS From October 2008 to December 2014, the German Embryotox Pharmacovigilance Centre identified 63 exposed pregnancies among 94 requests concerning rivaroxaban use during childbearing age. Follow-up included paediatric checks until 6 weeks after birth. RESULTS All pregnancies with completed follow-up were exposed at least during the first trimester. Treatment indications included venous thromboembolism, knee surgery, and atrial fibrillation. 37 pregnancies were prospectively ascertained and resulted in six spontaneous abortions, eight elective terminations of pregnancy, and 23 live births. All women had discontinued rivaroxaban after recognition of pregnancy, mostly in the first trimester, but in one woman treatment continued until gestational week 26. There was one major malformation (conotruncal cardiac defect) among the 37 prospectively ascertained pregnancies in a woman with complex medication and a previous foetus with cardiac malformation without exposure to rivaroxaban. Only one case of bleeding concerning a retrospective report of surgery for missed abortion was observed in our case series. CONCLUSION Our results might give reassurance to those women, who were inadvertently exposed to rivaroxaban in early pregnancy. However, our limited cohort size does not allow ruling out an increased malformation risk and does not support the use of rivaroxaban during pregnancy. In all cases of (inadvertent) rivaroxaban exposure during 1st trimester, anticoagulation regimen should be reconsidered and a detailed ultrasound assessment recommended to confirm normal foetal development.

Database: Medline
14. Efficacy and safety of direct oral anticoagulants during pregnancy; a systematic literature review

Author(s): Lameijer H.; Aalberts J.J.J.; van Veldhuisen D.J.; Pieper P.G.; Meijer K.

Source: Thrombosis Research; Sep 2018; vol. 169; p. 123-127

Publication Date: Sep 2018

Publication Type(s): Short Survey

PubMedID: 30036784

Abstract: Introduction: Direct oral anticoagulants (DOACs) are increasingly used for anticoagulation or prevention of thromboembolic events in conditions that may co-occur with pregnancy. However, evidence regarding efficacy and safety during pregnancy is scarce. Aim(s): To review the current literature concerning the efficacy, safety and outcome of DOACs during pregnancy in humans.

Method(s): We systematically searched the MedLine public database for all studies describing the use of DOACs during pregnancy published up to July 4th 2017. Result(s): 236 cases of DOAC use during pregnancy were reported. Rivaroxaban was the most reported DOAC (n = 178). DOACs were mostly used for prophylaxis or treatment of venous thromboembolism (n = 91). DOACs were discontinued within the first 2 months of pregnancy in 84%, maximum reported duration of use was 26 weeks. Pregnancy outcome data were available for 140 pregnancies. Thirty-nine pregnancies were electively terminated. In the remaining 101 pregnancies total miscarriage rate was 31% (n = 31) and live birth rate was 68% (n = 69, 1 missing). Foetal and neonatal abnormalities were reported in 8 pregnancies, of which at least half were suspected to be related to rivaroxaban use during the 1st trimester of pregnancy. In only 18% of cases (n = 42), the presence or absence of thrombotic and bleeding complications was reported. Conclusion(s): The limited available evidence raises concern regarding embryo-foetal safety, with high incidence of miscarriages and a 4% rate of anomalies with the use of rivaroxaban. Not enough data are available to judge safety and efficacy of the use of DOACs during pregnancy. Copyright © 2018

Database: EMBASE
15. 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

**PubMedID:** 26780747

Available at [Journal of Thrombosis and Thrombolysis](https://www.proquest.com) - NHS Version

Available at [Journal of Thrombosis and Thrombolysis](https://link.springer.com) - SpringerLink

**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).

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