ORIGINAL ARTICLE

A systematic review on the use of new anticoagulants in pregnancy

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Summary: 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*.

Keywords: anticoagulants, direct factor Xa inhibitors, direct thrombin inhibitors, pregnancy

INTRODUCTION

Anticoagulants (ACs) are commonly used in pregnancy for prevention and management of thrombotic problems. Pregnancy itself is a physiological procoagulant state and increases the risk of thrombosis. Venous thromboembolism (VTE) remains an important cause of maternal morbidity and mortality although in recent years there has been a decline of maternal deaths associated with VTE, likely due to better recognition of women at risk, and increasing use of thromboprophylaxis in this group of women.[1]

The main therapeutic agent recommended for use in the prevention and treatment of VTE in pregnancy is low molecular weight heparin (LMWH),[2,3] which has largely replaced standard, unfractionated heparin (UFH). Neither of these agents cross the placenta and are safe in pregnancy.[4] However, heparin therapy could result in adverse reactions such as heparin-induced thrombocytopaenia (HIT) – an immune reaction where antibodies are developed against complexes of platelet factor 4 and heparin on platelet surfaces (anti-HP4 antibodies), leading to a platelet count fall of >50% and thrombotic complications, cutaneous reactions ranging from a local rash at the injection site to disseminated plaques, or osteopaenia.[3–5] When these occur, alternative forms of ACs are required.

Highly effective and established ACs are vitamin K antagonists (VKA) such as warfarin, but these cross the placenta and anticoagulate the fetus. They are best avoided in pregnancy due to their association with adverse pregnancy outcomes including miscarriage, prematurity, lower birth weight, neurodevelopmental problems and fetal bleeding, as well as a risk of major birth defects with first trimester exposure.[2,6] Furthermore, VKA have a slow onset of action, have multiple food and drug interactions and require monitoring due to genetic variations in metabolism.[7] Other available forms of anticoagulation include danaparoid, a low molecular weight heparinoid.[2] Danaparoid neither crosses the placenta nor is secreted in breast milk and thus is theoretically safe in pregnancy.[8] The quest for the ideal form of anticoagulation with rapid onset, preferably not parenterally administered, stable pharmacokinetic and pharmacodynamic properties, leading to less interaction with other drugs or food, and less need for constant monitoring, has led to the development of new ACs. The major classes of new ACs are direct factor Xa inhibitors and direct thrombin inhibitors (DTIs). These have different mechanisms of action from the heparins and VKA. Factor Xa appears to be a good target as it is positioned in the convergence of the extrinsic and intrinsic pathways of coagulation. When activated, one molecule of factor Xa generates more than 1000 thrombin molecules.[9] Thrombin (factor II) is also a logical target as it converts fibrinogen to fibrin and amplifies its own generation by feedback activation of factors V, VIII and IX.[9] Thus, inhibition of factor Xa and/or thrombin would have an anticoagulation effect by reducing thrombin generation and interaction, and fibrin formation (Figure 1).

Fondaparinux, the first selective factor Xa inhibitor, is a synthetic analogue of the antithrombin-binding pentasaccharide which interacts with antithrombin and factor Xa for anticoagulant effects. It is licensed for use in the treatment and prevention of VTE outside of pregnancy.[10] Its effectiveness paved the way in the development of a direct Factor Xa inhibitor. Fondaparinux, like the heparins, is administered by subcutaneous

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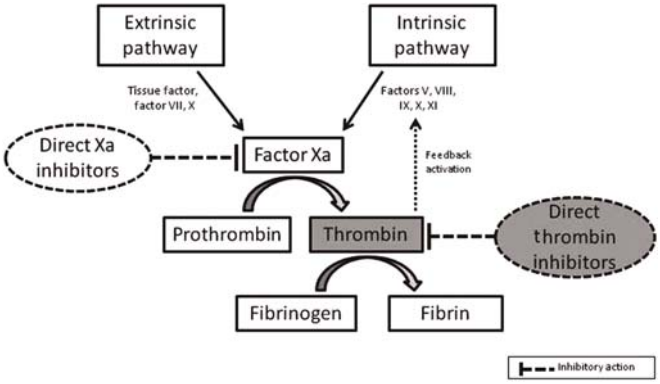

Figure 1 **Mechanisms of action of the newer oral anticoagulants**

injections, which is inconvenient for long-term use. The new direct factor Xa inhibitors such as rivaroxaban, apixaban and betrixaban are administered orally, which is a significant advantage. These are currently being introduced to practice following clinical trials with good efficacy similar to the heparins.

Recombinant hirudin (lepirudin) and argatroban were the initial DTIs manufactured and licensed for prophylaxis or treatment of thrombosis in patients diagnosed with HIT.[11] Both these are administered parenterally. The first oral DTI was ximelagatran, which was launched for use in the prophylaxis of VTE after extensive phase III trials (METHRO III, EXPRESS trial, EXULT-A and B).[12] Unfortunately, this was quickly followed by its withdrawal due to potential hepatotoxicity.[13] Nevertheless, the efficacy of ximelagatran allowed for the development of further DTIs such as dabigatran, which is currently being evaluated in clinical trials.[12]

The evaluation of these new oral ACs have mostly been in the thromboprophylaxis and treatment of VTE after orthopaedic surgery, and medical uses such as treatment of acute coronary syndrome (ACS), or the prevention of stroke in atrial fibrillation (AF) and with mechanical heart valves.[12,14,15] To date, most trials have shown that these newer ACs have efficacy similar to LMWH or warfarin.[12,14,15] The experience and use of these new ACs for prophylaxis or treatment of VTE in pregnancy is, however, limited, and needs to be investigated as the benefit and use of any medication in pregnancy is balanced by the potential risk of fetal toxicity particularly as orally active agents usually cross the placenta .

This review therefore aims to systematically search for all published studies or case reports on the use of these newer ACs, either for prophylactic or therapeutic purposes, in women who are pregnant or who are in the immediate postnatal period. Apart from assessing the number of cases reported, the indication, method for dose monitoring in pregnancy if relevant, special requirements for regional anaesthesia, pregnancy outcomes and complications secondary to these anticoagulants use will also be assessed.

METHODS

A systematic review of newer AC use in pregnancy was performed by searching the electronic databases MEDLINE (from 1966), EMBASE (from 1974) and the Cochrane Library up to October 2011. Searches in the Cochrane Library include the Cochrane Database of Systematic Reviews (Cochrane reviews), Database of Abstracts of Reviews of Effects (other reviews), Cochrane Central Register of Controlled Trials (clinical trials), Health Technology Assessment Database (technology assessments) and NHS Economic Evaluation Database (economic evaluations). The search was undertaken by the Royal Society of Medicine with the use of an automatic duplicate checker to remove duplicate records retrieved from different databases. The search included terms of 'new anticoagulants', 'pregnancy', 'puerperium' and 'breastfeeding'. The MeSH terms 'pregnancy', 'pregnancy complications', 'postpartum period', 'puerperal disorders', 'lactation', 'lactation disorders' and 'venous thrombosis' were exploded to include all relevant citations. The ACs searched were 'fondaparinux', 'dabigatran', 'flovagatran', 'pegmusirudin', 'ximelagatran', 'melagatran', 'rivaroxaban', 'apixaban', 'betrixaban', 'eribaxaban', 'idraparinux', 'idrabiotaparinux' and 'otamixaban'. The references of full text articles retrieved were also reviewed for relevant studies. Subsequently, the clinical trial registers were searched to assess if pregnancy was an inclusion or exclusion criteria of recruitment into randomized controlled trials (RCT) of these new ACs.

All citations reporting on the use of new ACs in pregnancy, breastfeeding and postnatal period (up to 6 weeks) for thromboprophylaxis or treatment of VTE were considered relevant for this review. This included clinical trials, case reports, letters, abstracts and review articles. Publications that were reporting on new AC use outside of pregnancy, clinical trials of new ACs where pregnancy and breastfeeding were exclusion criteria, and review articles with no examples of new AC use in pregnancy were excluded from the review. The selection process of the included citations is shown in Figure 2.

Information on the experience of AC use was recorded. This included the type of AC used, the indication for use, previous AC use and reasons for switching, dose requirement in the antenatal, intrapartum and postnatal period, the need for monitoring in pregnancy, precautions taken for regional anaesthesia, the pregnancy outcome, complications of bleeding or adverse reactions and issues surrounding breastfeeding. It was anticipated that the majority of included citations would be case reports and thus no pooling of results was planned, and results were tabulated.

RESULTS

The search yielded 561 citations, of which 432 were excluded after reading the abstracts (Figure 2). Clinical trials register were then assessed to exclude trials published in the Cochrane library where the exclusion criteria were women who were pregnant or breastfeeding. This excluded 59 citations. Full text articles were retrieved for 70 citations for in-depth analysis. A review of the reference lists of these articles added another four relevant citations.[16–19] From these, 63 citations were excluded for the reasons listed in Figure 2. There were 10 trials in the Cochrane database that were not relevant, two letters[20,21] were excluded as they were responses to a published case report,[22] three[17,19,23] reported on women who were not pregnant and another 48 were review articles on new ACs with no description of new cases not already included in the search. In total, 11 articles were included in this review. There were 10 publications on fondaparinux use (24 pregnancies), and one reported on a study of excretion of ximelagatran in breast milk. There were no reports of the use of other selective

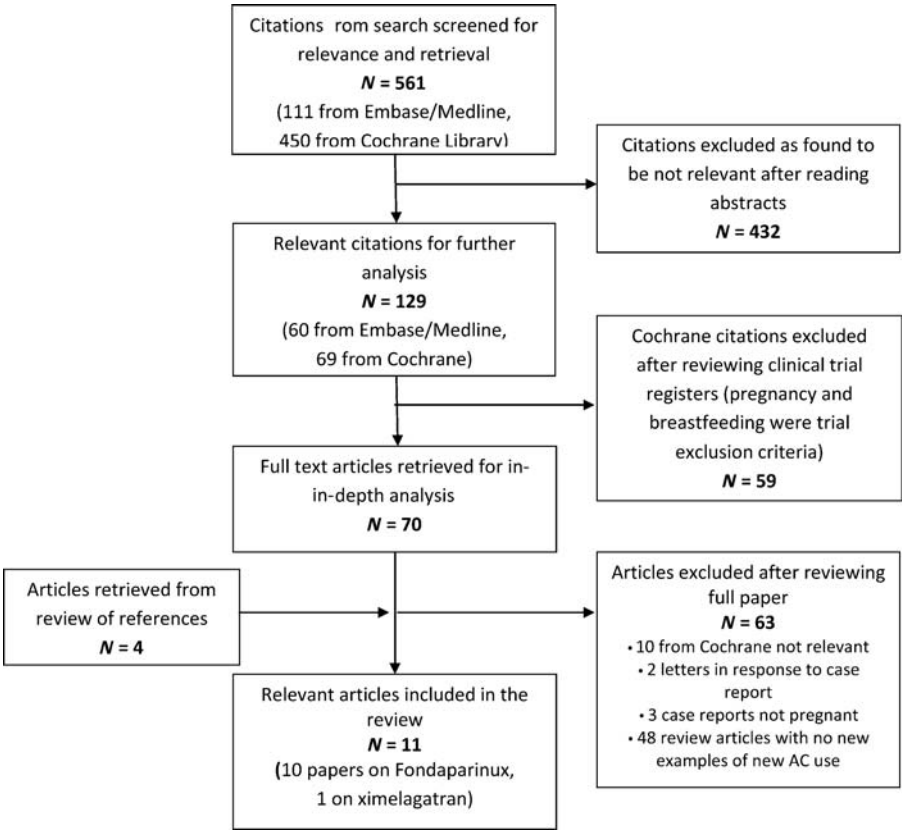

Figure 2 **Selection process of included citations**

Xa inhibitor administered parenterally such as idraparinux and idrabiotaparinux, or any new oral ACs such as rivaroxaban, apixaban or dabigatran in pregnancy or the puerperium.

There were 10 publications which reported the use of fondaparinux in 24 pregnant women. Of these, seven were for thromboprophylaxis for previous VTE and other medical conditions at risk of thrombosis such as thrombophilia or antiphospholipid syndrome (APS)[16,22,24–28] (Table 1), and three were for treatment of VTE[18,29,30] (Table 2). The commonly used dose for thromboprophylaxis was 2.5 mg once daily. All used fondaparinux as an alternative AC in women who had previously developed skin reactions to UFH or LMWH. The largest case series of 10 women was published by Knol *et al.*[28] They reported that three women had an estimated blood loss of greater than 1000 mL at delivery, but no blood transfusion was required. Apart from these cases, there were no other reports of bleeding complications. The majority of the cases reported stopping fondaparinux at least 24 hours prior to regional anaesthesia with no problems. The half-life of fondaparinux is 17–24 hours. There was one case of preterm emergency caesarean section at 34/40 gestation for intrauterine growth restriction (IUGR),[26] but this woman was known to have both systemic lupus erythematosis and APS, which could have accounted for the observed growth restriction. All other publications reported the delivery of a healthy baby at term, or reported that there were no adverse pregnancy outcomes. The commonly used treatment dose of fondaparinux was 7.5 mg once daily (Table 2). In two cases,[29,30] fondaparinux was prescribed as the women were confirmed to have HIT with the presence of antiplatelet–heparin binding antibodies and anticoagulation was needed for treatment of pulmonary embolism. In all cases, fondaparinux was stopped 24 hours prior to regional anaesthesia and there were no reported pregnancy complications.

One study examined the excretion of ximelagatran in breastmilk published in 2005[31] before the risk of hepatotoxicity with ximelagatran was confirmed and the drug withdrawn from the market. This study showed only trace amounts of ximelagatran and its intermediates in breast milk 72 hours after oral intake and concluded that exposure of breast-fed babies to this drug was not of clinical concern.

There were no published case reports of newer oral AC use such as rivaroxaban, apixaban, betrixaban or dabigatran, in pregnancy or the puerperium.

DISCUSSION

The new oral ACs have significant advantages over the heparins and VKA, with reduced need for monitoring and being available as oral preparations. However, the experience and safety in pregnancy is currently unknown with no report of use in pregnancy or the puerperium. These oral ACs are mostly in advanced stages of development and clinical trials in the prophylaxis and treatment of VTE in orthopaedic surgery patients and medical patients for prevention of stroke in AF or secondary prevention for patients with ACS.[12,14,15] Due to the unknown risk of these medications in pregnancy and puerperium and the likelihood of them crossing the placenta, pregnancy testing may be needed prior to prescribing these ACs, and women should be on effective contraception while on these drugs. In view of the lack of pregnancy data, it would be inappropriate to include women who are pregnant

Table 1 **The reported thromboprophylactic use of Factor Xa inhibitors in pregnancy**

Author	*N*	Indication for therapy	Indication for new ACs	Therapy (dose, duration)	Intrapartum	Complications	Pregnancy outcome
Fondaparinux							
Dempfle[16]	5	Prophylaxis for thrombophilia or previous VTE	All skin reactions	2.5 mg OD		None	No adverse outcomes
Wijesiriwardana[24]	1	Prophylaxis for previous DVT in pregnancy	Skin reaction to Daltaparin and Enoxaparin	Antenatal: Warfarin 13/40–36/40 2.5 mg OD Fondaparinux from 36/40 Postpartum: 2.5 mg 6 hours postnatal and warfarin thereafter	Stopped day of IOL	None EBL 300 mL	IOL at 39/40 LB boy, BW 3.57 kg No problems
Mazzolai[25]	1	Prophylaxis for previous DVT	Skin reaction to heparin and danaparoid	2.5 mg OD from early pregnancy (monitored anti-Xa activity)	Stopped 24 hours before CS	None	CS Healthy baby
Harenberg[26]	1	Prophylaxis for previous VTE, known SLE and APS	Skin reaction	2.5 mg OD prior to pregnancy and throughout (also 100 mg aspirin) (monitored anti-Xa activity) Postpartum: 2.5 mg OD and then converted to warfarin	Stopped day before, no mention of analgesia	IUGR, no mention of bleeding	CS at 34/40, IUGR, normal APGARS
Gerhardt[27]	2	Prophylaxis for previous VTE and PE	Skin reaction	2.5 mg OD (4/52 years fondaparinux levels) and until 6/52 postpartum 2nd case still pregnant at 26/40 at report	24 hours before CS	None	39/40 elective CS for PET, the other patient was 26/40 pregnant at the time of publication
Aiono-Le-Tagaloa[22]	1	Prophylaxis for APS and SLE	No mention	7.5 mg OD	Epidural 48 hours after last dose	None	IOL, Emergency CS. No mention of fetal outcome, but discharged home day 5 with no problems
Knol[28]	10 (but 12 pregnancies)	Prophylaxis for VTE	All skin reactions to tinzaparin or nadroparin	2.5 mg BD (No monitoring)	No mention	3/10 EBL >1000 mL, no transfusion needed No side-effects	Mean age at delivery 39/40, mean BW 3685 g, No fetal abnormalities or bleeding problems

VTE, venous thromboembolism; OD, once daily; DVT, deep vein thrombosis; IOL, induction of labour; EBL, estimated blood loss; LB, livebirth; CS, caesarean section; SLE, systemic lupus erythromatosus; APS, antiphospholipid syndrome; IUGR, intrauterine growth restriction; PET, pre-eclampsia; BD, twice daily; PE, pulmonary embolism; BW, birthweight

Table 2 The reported therapeutic use of Factor Xa inhibitors in pregnancy

Author	N	Indication for therapy	Indication for new ACs	Therapy (dose, duration)	Intrapartum	Complications	Pregnancy outcome
Fondaparinux							
Schapkaitz[18]	1	Treatment for PE at 16/40 with twins, changed to Fondaparinux 28/40	Skin reaction to both enoxaparin and nadroparin	2.5 mg OD (No monitoring)	No mention, but stopped 24 hours b4 CS	None	Elective CS, healthy LB × 2, 2.2 and 2.4 kg
Hajj-Chahine[29]	1	Treatment for PE at 25/40, previous DVT and given enoxaparin prophylaxis	HIT	7.5 mg OD (No mention of monitoring) Had surgical embolectomy and then continued 7.5 mg rest of pregnancy Postpartum: 7.5 mg OD and warfarin therafter	Stopped 24 hours before IOL	None	IOL, LB at 38/40, no problems
Ciurzynski[30]	1	Treatment for PE at 34/40, started UFH	HIT	7.5 mg OD (monitored platelets as was very low with HIT) Postnatal: 7.5 mg given on 1st day post op and warfarin thereafter	Stopped 24 hours before CS	None	37/40 elective CS, no problems with baby

PE, pulmonary embolism; OD, once daily; CS, caesarean section; DVT, deep vein thrombosis; HIT, heparin induced thrombocytopaenia; IOL, induction of labour; LB, livebirth; UFH, unfractionated heparin

or breastfeeding in clinical trials. Thus, it was not surprising that clinical trials of selective Xa inhibitors such as Equinox and MATISSE, Factor Xa inhibitors such as EXPLORE Xa, ODIXa, Botticelli and Einstein, and DTI trials such as RECOVER have all excluded women who were at risk of getting pregnant, were pregnant or were breastfeeding (www.clinicaltrials.org.uk).

Currently, alternative ACs include danaparoid, hirudin, argatroban and fondaparinux which are not licensed for use in pregnancy. There is currently limited evidence of their safety. Danaparoid is a heparinoid with both anti-Xa and antithrombin effects .It neither crosses the placenta nor is secreted in breast milk and is thus theoretically safe in pregnancy for the fetus. A review of the literature from 1981 and 2004 by Lindhoff-Last E *et al.*[8] reported use of danaparoid in 51 pregnancies with heparin intolerance (32 due to HIT, 19 due to skin rash) with no adverse pregnancy effects. In this review, the danaparoid dose regimens ranged from 1000 to 7500 U/day with a median duration use of 10 weeks. They reported four maternal bleeding events and three fetal death, all associated with maternal complications prior to danaparoid use.[8] Danaparoid neither crosses the placenta nor is secreted in breast milk. As this is a heparinoid, there remains the (remote) possibility of HIT due to the risk of positive cross-reactivities with antibodies to danaparoid. It is the ACs recommended by the American College of Chest Physicians for use in pregnancy when intolerance to heparin such as HIT occurred.[32] They recommend that DTIs be used only in situations of severe reaction to heparin and danaparoid is not tolerated.[2]

To date, two types of DTI, R-hirudin and argatroban have been used in pregnancy (Table 3). They are both administered parenterally. There are case reports of hirudin use with minimal complications of bleeding.[33–37] Animal studies have shown minimal placental transfer of hirudin to the fetus,[38] which could be extrapolated to being safe in human pregnancy. There were cases where premature delivery was indicated but it was for reasons that were not related to AC use.[33,35] As with UFH/LMWH, there is a risk of developing anti-hirudin antibodies when hirudin is used long term. There were three cases[39–41] of reported argatroban use, all for the treatment of thrombosis in pregnancy, after the diagnosis of HIT to UFH or LMWH. There were no reports of bleeding complications. Regional analgesia was used in the two cases at least two hours after stopping the argatroban infusion, with no reported complications. In all the cases, there was a livebirth. Young *et al.*[40] reported that the baby had a congenital abnormality of a ventricular septal defect and patent foramen ovale, but these are abnormalities during organogenesis in the first trimester which is not consistent with a relationship to argatroban.

Fondaparinux, the synthetic pentasaccharide, is recommended for use by the Pregnancy and Thrombosis Working Group in cases when HIT occur in pregnancy as it does not cross the placenta and is an FDA Class B medication[42]/Australian Category C. The recommended dose was 2.5 mg once daily for prophylactic use and was weight-dependent when used for treatment of thrombosis (5 mg once daily if <50 kg, 7.5 mg if 50–100 kg, 10 mg if >100 kg). Furthermore, in addition to the cases described in this review where outcomes have been favourable, there is a study, FondaPPP initiated by the manufacturers of fondaparinux, that collected information on 120 women who used fondaparinux around the time of pregnancy, and it has shown no adverse outcomes (www.gsk-clinicalstudyregister.com).

Table 3 **Examples of newer anticoagulants use in pregnancy**

Author	N	Indication for therapy (thromboprophylaxis or treatment)	Indication for new ACs	Therapy (dose, duration)	Intrapartum	Complications	Pregnancy outcome
R-Hirudin (Lepirudin)							
Huhle[33]	1	Prophylaxis for recurrent VTE, known SLE	HIT on dalteparin at 25/40	Antepartum: 15 mg BD, maintained at aPTT 1.5× Postpartum: 25 mg BD for 10/7, then 30 mg BD for 3/52 for aPTT 2–2.5×, then vitamin K antagonist long term	No mention	No abnormal bleeding	Emergency CS at 26/40 for PET and suboptimal CTG, female LB, BW 500 g, NNU due to RDS
Mehta[34]	1	Prophylaxis then treatment for PE at 7/40	Skin reaction to Enoxaparin, UFH and Tinzaparin and HIT	Lepirudin infusion, then 50 mg BD, to 125 mg BD (aPTT 2–2.5 weekly), converted to warfarin at 15/40 as did not want injections Postnatal: IV lepirudin then warfarin long term	Converted to IV lepirudin at 38/40	No mention	Elective CS of healthy baby at 38/40
Harenberg[35]	1	Prophylaxis for recurrent VTE, known APS and Lupus	Heparin allergy (skin reactions)	Lepirudin 25 mg BD and aspirin (monitored with aPTT) Switched to IV lepirudin at 29/40 Postnatal: 25 mg BD, then warfarin long term	Switched to IV infusion 7/7 before CS	None	Emergency CS at 30/40 for severe lupus symptoms, LB male baby, BW 1050 g,
Aijaz[36]	1	Treatment for DVT at 24/40, was on aspirin as previous VTE	Heparin allergy (skin reaction) from previous UFH treatment	r-Hirudin loading dose 0.4/kg, then infusion of 0.15 mg/kg/hour (aPTT 2×) for 2/7, then switched to warfarin (INR 2-.5) Postnatal: r-Hirudin (aPTT 2×) for 36 hours, then warfarin long term	Warfarin stopped 4/7 before IOL (no mention of regional anaesthesia)	None	IOL at term, NVD of healthy baby
Hiwarkar (postnatal)[37]	1	Treatment of DVT in illio-femoral and popliteal veins 10/7 postpartum, then PE in 6/52, known Behcet's disease	Thrombus resistant to treatment of dalteparin and warfarin, convert to lepirudin	Lepirudin dose to maintain aPTT 1.5–2.5, then pt thrombolysed with streptokinase, then switched to fondaparinux 7.5 mg OD	NA	No mention	10/7 postnatal
Argatroban							
Ekbatani[39]	1	Treatment of DVT in brachial and basilic veins, 18/40 gestation	HIT to UFH	Antepartum: Argatroban (aPTT 1.5× above normal) Fondaparinux 7.5 g OD after clot resolved Intrapartum: Argatroban infusion 2 μg/kg/min Postpartum: Fondaparinux 7.5 mg OD Warfarin thereafter	Combined spinal-Epidural 50 hours after fondaparinux, 2 hours after argatroban infusion stopped	None EBL at delivery <400 mL	IOL, LB, Male, BW 3.8 kg Normal cord pH
Young[40]	1	Treatment of portal vein thrombosis at 31/30, changed at 33/30	HIT while on enoxaparin (but later diagnosis ITP)	Antepartum: Argatroban 2–8 μg/kg/min (monitor aPTT 50–77 s) No mention of post-natal regime	Argatroban stopped morning of IOL, epidural after 7 hours		IOL at 39/40, Male, Normal APGARS, BW 3092 g, VSD and PFO at birth, at 6/12 FU, only PFO
Taniguc[41]hi S	1	Treatment of PE at 22/40, already had DVT at 18/40 and was on UFH then danaparoid, but platelets dropped	Possible HIT or myelodysplastic syndrome	Argatroban use during pulmonary embolectomy Intraop: Bolus of 0.1 mg/kg, then infusion of 5–10 ug/kg/min (monitor clotting time >350 s) No mention of post-op or post-natal anticoagulation	No mention	No mention (but gave FFP and platelets prophylactically post-op to minimize bleeding	Emergency CS at 29/40, healthy baby

VTE, venous thromboembolism; SLE, systemic lupus erythromatosus; HIT, heparin induced thrombocytopaenia; BD, twice daily; aPTT, activated partial thromboplastin time; CS, caesarean section; PET, pre-eclampsia; CTG, cardiotocograph; LB, livebirth; BW, birthweight NNU-neonatal unit; RDS, respiratory distress syndrome; PE, pulmonary embolism; UFH, unfractionated heparin; IV, intravenous; APS, antiphospholipid syndrome; DVT, deep vein thrombosis; IOL, induction of labour; NVD, normal vaginal delivery; EBL, estimated blood loss; OD, once daily; ITP, immune thrombocytopaenic purpura; VSD, ventricular septal defect; PFO, patent foramen ovale; FU, follow-up; FFP, fresh frozen plasma

Newer ACs such as fondaparinux and danaparoid on the current limited evidence appear to have no adverse pregnancy outcomes. However, more information about safety in pregnancy is needed for lepirudin and argatroban All these new ACs appear effective as there was no recurrence of thrombosis when used therapeutically, and no thrombotic events when used prophylactically. However, in view of the extensive experience with LMWH and its safety and efficacy in pregnancy, there may be little perceived advantage from these newer parenterally administered agents in the routine management of thrombotic problems in pregnancy.

While the new oral ACs are more attractive than parenteral preparations for long-term use, these are likely to cross the placenta and pose problems for the fetus. Such concern may explain the lack of data on the new oral AC use in pregnancy as the risks to the developing and maturing fetus *in utero* are unknown. Experience is likely to grow as these preparations become widely used and reports of accidental exposure in pregnancy are published Further research is required examining their pharmacokinetic properties, placental transfer and risk of teratogenicity, prior to initiating use of these medications in pregnancy.

The postnatal period is the time of highest risk of VTE. For women at high risk of thromboembolism or following an acute VTE in pregnancy, ACs are continued for at least six weeks postpartum.[2,3,43] Warfarin is suitable for use in the postnatal period. Women on parenteral ACs can be converted to warfarin when the risk of obstetric haemorrhage is low, commonly about days 5–7 after the delivery of the baby.[3] It is not contraindicated in breastfeeding. Studies similar to that carried out on ximelagatran[31] investigating the clearance and excretion of these new oral ACs and their metabolites into breast milk are required prior to recommending use of these medications in breastfeeding and the postnatal period.

CONCLUSION

The development of new oral AC provides advantages in the field of orthopaedics and general medicine, but there is still no experience of their use in pregnancy. Thus, until more evidence is available, these new oral ACs should not be used in the field of obstetrics when there are alternatives available. If there are no alternatives, women need to be counselled about the lack of information, and potential risks of harm of these new oral ACs. However, experience is likely to grow when inadvertent exposure of these oral ACs in pregnancy occurs. There is a need for reporting on accidental use of new ACs and cases if new oral ACs were used in pregnancy in situations where women have adverse reactions to UFH or LMWH, and have not been able to tolerate parenteral ACs such as danaparoid, hirudin, argatroban or fondaparinux. This will allow for more information about the safety and risks of these new oral ACs to the fetus and to provide alternative options when these are needed.

DECLARATION

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Ethical approval: Ethical approval was not needed for this review.
Guarantor: IAG.
Contributorship: AWT and IAG read the papers and identified suitable studies for inclusion. AWT wrote the initial draft and IAG revised the manuscript.
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REFERENCES

1 Cantwell R, Clutton-Brock T, Cooper G, *et al*. Saving mothers' lives: reviewing maternal deaths to make motherhood safer: 2006–2008. The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. *BJOG* 2011;**118**(Suppl. 1):1–203
2 Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos AM, Vandvik PO. 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* 2012;**141**(Suppl):e691S–736S
3 The acute management of thrombosis and embolism during pregnancy and the puerperium. *RCOG Greentop Guidelines* No 37b. 2010 (http://www.rcog.org.uk/files/rcog-corp/GTG37b_230611.pdf)
4 Greer IA, Nelson-Piercy C. Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy. *Blood* 2005;**106**:401–7
5 Alban S. Adverse effects of heparin. *Handb Exp Pharmacol* 2012;**207**:211–63
6 Schaefer C, Hannemann D, Meister R, *et al*. Vitamin K antagonists and pregnancy outcome. A multi-centre prospective study. *Thromb Haemost* 2006;**95**:949–57
7 Anand SS, Yusuf S. Oral anticoagulant therapy in patients with coronary artery disease: a meta-analysis. *JAMA* 1999;**282**:2058–67
8 Lindhoff-Last E, Kreutzenbeck HJ, Magnani HN. Treatment of 51 pregnancies with danaparoid because of heparin intolerance. *Thromb Haemost* 2005;**93**:63–9
9 Mann KG, Brummel K, Butenas S. What is all that thrombin for? *J Thromb Haemost* 2003;**1**:1504–14
10 Turpie AG, Bauer KA, Eriksson BI, Lassen MR. Fondaparinux vs enoxaparin for the prevention of venous thromboembolism in major orthopedic surgery: a meta-analysis of 4 randomized double-blind studies. *Arch Intern Med* 2002;**162**:1833–40
11 Di Nisio M, Middeldorp S, Buller HR. Direct thrombin inhibitors. *N Engl J Med* 2005;**353**:1028–40
12 Mehta RS. Novel oral anticoagulants. Part II: direct thrombin inhibitors. *Expert Rev Hematol* 2010;**3**:351–61
13 Testa L, Andreotti F, Biondi Zoccai GG, Burzotta F, Bellocci F, Crea F. Ximelagatran/melagatran against conventional anticoagulation: a meta-analysis based on 22,639 patients. *Int J Cardiol* 2007;**122**:117–24
14 Mehta RS. Novel oral anticoagulants for prophylaxis and treatment of venous thromboembolism: part I (Factor Xa inhibitors). *Expert Rev Hematol* 2010;**3**:227–41
15 Weitz JI, Eikelboom JW, Samama MM. New antithrombotic drugs: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;**141**(Suppl):e120S–151S
16 Dempfle CE. Minor transplacental passage of fondaparinux in vivo. *N Engl J Med* 2004;**350**:1914–5
17 Jappe U, Juschka U, Kuner N, Hausen BM, Krohn K. Fondaparinux: a suitable alternative in cases of delayed-type allergy to heparins and semisynthetic heparinoids? A study of 7 cases. *Contact Dermatitis* 2004;**51**:67–72
18 Schapkaitz E, Jacobson BF. Delayed hypersensitivity to low-molecular-weight heparin (LMWH) in pregnancy. *S Afr Med J* 2007;**97**:1255–7
19 Maetzke J, Hinrichs R, Staib G, Scharffetter-Kochanek K. Fondaparinux as a novel therapeutic alternative in a patient with heparin allergy. *Allergy* 2004;**59**:237–8
20 Gogarten W. Fondaparinux and epidural anaesthesia. *Int J Obstet Anesth* 2009;**18**:288; author reply 290
21 Llau JV. Epidural labor analgesia in a patient receiving fondaparinux. *Int J Obstet Anesth* 2009;**18**:288–9; author reply 290
22 Aiono-Le Tagaloa L, Carvalho B. Epidural labor analgesia in a patient receiving fondaparinux. *Int J Obstet Anesth* 2009;**18**:94–5
23 Parody R, Oliver A, Souto JC, Fontcuberta J. Fondaparinux (ARIXTRA) as an alternative anti-thrombotic prophylaxis when there is hypersensitivity to low molecular weight and unfractionated heparins. *Haematologica* 2003;**88**:ECR32

24 Wijesiriwardana A, Lees DA, Lush C. Fondaparinux as anticoagulant in a pregnant woman with heparin allergy. *Blood Coagul Fibrinolysis* 2006;**17**:147–9
25 Mazzolai L, Hohlfeld P, Spertini F, Hayoz D, Schapira M, Duchosal MA. Fondaparinux is a safe alternative in case of heparin intolerance during pregnancy. *Blood* 2006;**108**:1569–70
26 Harenberg J. Treatment of a woman with lupus and thromboembolism and cutaneous intolerance to heparins using fondaparinux during pregnancy. *Thromb Res* 2007;**119**:385–8
27 Gerhardt A, Zotz RB, Stockschlaeder M, Scharf RE. Fondaparinux is an effective alternative anticoagulant in pregnant women with high risk of venous thromboembolism and intolerance to low-molecular-weight heparins and heparinoids. *Thromb Haemost* 2007;**97**:496–7
28 Knol HM, Schultinge L, Erwich JJ, Meijer K. Fondaparinux as an alternative anticoagulant therapy during pregnancy. *J Thromb Haemost* 2010;**8**:1876–9
29 Hajj-Chahine J, Jayle C, Tomasi J, Corbi P. Successful surgical management of massive pulmonary embolism during the second trimester in a parturient with heparin-induced thrombocytopenia. *Interact Cardiovasc Thorac Surg* 2010;**11**:679–81
30 Ciurzynski M, Jankowski K, Pietrzak B, *et al.* Use of fondaparinux in a pregnant woman with pulmonary embolism and heparin-induced thrombocytopenia. *Med Sci Monit* 2011;**17**:CS56–59
31 Hellgren M, Johansson S, Eriksson UG, Wahlander K. The oral direct thrombin inhibitor, ximelagatran, an alternative for anticoagulant treatment during the puerperium and lactation. *BJOG* 2005;**112**:579–83
32 Warkentin TE, Greinacher A, Koster A, Lincoff AM. Treatment and prevention of heparin-induced thrombocytopenia: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008;**133**(6 Suppl):340S–80S
33 Huhle G, Geberth M, Hoffmann U, Heene DL, Harenberg J. Management of heparin-associated thrombocytopenia in pregnancy with subcutaneous r-hirudin. *Gynecol Obstet Invest* 2000;**49**:67–9
34 Mehta R, Golichowski A. Treatment of heparin induced thrombocytopenia and thrombosis during the first trimester of pregnancy. *J Thromb Haemost* 2004;**2**:1665–6
35 Harenberg J, Jorg I, Bayerl C, Fiehn C. Treatment of a woman with lupus pernio, thrombosis and cutaneous intolerance to heparins using lepirudin during pregnancy. *Lupus* 2005;**14**:411–2
36 Aijaz A, Nelson J, Naseer N. Management of heparin allergy in pregnancy. *Am J Hematol* 2001;**67**:268–9
37 Hiwarkar P, Stasi R, Sutherland G, Shannon M. Deep vein and intracardiac thrombosis during the post-partum period in Behcet's disease. *Int J Hematol* 2010;**91**:679–86
38 Markwardt F, Fink G, Kaiser B, *et al.* Pharmacological survey of recombinant hirudin. *Pharmazie* 1988;**43**:202–7
39 Ekbatani A, Asaro LR, Malinow AM. Anticoagulation with argatroban in a parturient with heparin-induced thrombocytopenia. *Int J Obstet Anesth* 2010;**19**:82–7
40 Young SK, Al-Mondhiry HA, Vaida SJ, Ambrose A, Botti JJ. Successful use of argatroban during the third trimester of pregnancy: case report and review of the literature. *Pharmacotherapy* 2008;**28**:1531–6
41 Taniguchi S, Fukuda I, Minakawa M, Watanabe K, Daitoku K, Suzuki Y. Emergency pulmonary embolectomy during the second trimester of pregnancy: report of a case. *Surg Today* 2008;**38**:59–61
42 Duhl AJ, Paidas MJ, Ural SH, *et al.* Antithrombotic therapy and pregnancy: consensus report and recommendations for prevention and treatment of venous thromboembolism and adverse pregnancy outcomes. *Am J Obstet Gynecol* 2007;**197:457** e451–421
43 Reducing the risk of thrombosis and embolism during pregnancy and the puerperium. *RCOG Greentop Guidelines*. November 2009

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