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The use of fondaparinux in pregnancy

Venous thromboembolism (VTE) remains a major cause of morbidity and mortality in pregnancy. Although relatively safe, hypersensitivity reactions to low-molecular weight heparins (LMWHs) are frequently seen in pregnant women, with a reported 20% incidence in this cohort (Bank *et al*, 2003; Schindewolf *et al*, 2013). Fondaparinux is a synthetic pentasaccharide that has been extensively studied in thromboprophylaxis and treatment of VTE and which may be used as an alternative in these circumstances. This study describes the use of fondaparinux in pregnant women who experienced heparin allergy in our institution over an 8-year period.

Thirteen women and 15 pregnancies exposed to fondaparinux in the antepartum period were included in the study (Tables SI, SII). In all women, one or two LMWHs (tinzaparin, enoxaparin or dalteparin) were used prior to initiating fondaparinux. In 6 of 15 pregnancies, fondaparinux was commenced in the first trimester, 8/15 from the second trimester and the remaining 1/15 in the third trimester. Six of 15 pregnancies received prophylactic doses of fondaparinux (2·5 or 5 mg/d) and 9/15 pregnancies received treatment doses of fondaparinux (7·5 or 10 mg/d).

Of these 15 pregnancies, 10 were uncomplicated and resulted in healthy babies (defined as being the appropriate growth for gestational age and not preterm). The remaining five were 'complicated' meaning the course and/or the outcome of the pregnancy had difficulties. Of these, Patient 1 experienced a further VTE whilst on full treatment dose of fondaparinux. The recommended dose for this woman, who weighed 99 kg, was 7·5 mg/d, (10 mg is recommended for weight 100 kg) and the lower dose may be considered responsible for the second DVT (inadequate anticoagulation rather than treatment failure).

Of the five complicated pregnancies, two resulted in miscarriages and one patient had a termination of pregnancy due to fetal abnormalities. Patient 6 had a history of both recurrent VTE and miscarriage; she miscarried in the first

trimester whilst on fondaparinux. Patient 11 miscarried after 5 weeks exposure to fondaparinux; however 3 years later this patient had a normal pregnancy whilst being on fondaparinux from the first trimester onwards. Patient 5, who was started on fondaparinux during her first pregnancy at week seven, willingly terminated her first pregnancy at 23 weeks gestation due to fetal abnormalities (Tetralogy of Fallot and Dandy–Walker syndrome). She subsequently became pregnant again but opted to be managed with Tinzaparin and tolerate the skin lesions with antihistamines and topical steroids.

The remaining two complicated pregnancies had unfavourable outcomes. Patient 3, who had a dichorionic, diamniotic twin pregnancy, experienced premature spontaneous rupture of membranes at 22 weeks, further complicated by a cord prolapse. Only one twin survived after an extended period of neonatal intensive care. Fondaparinux is not believed to have played a role in this event.

Patient 13 highlights an important practical issue to consider when treating pregnant patients with fondaparinux. This pregnancy resulted in a child with cerebral palsy, which may have been due to lack of experience with management of fondaparinux around the time of delivery in a different hospital. She presented with reduced fetal movements and pathological cardiotocogram, necessitating emergency cesarean section. The surgery was, however, delayed because of concerns regarding maternal bleeding in a woman who had recently received fondaparinux.

Of the 12 viable pregnancies, there were seven normal vaginal deliveries, two forceps deliveries and three women required cesarean sections. During these deliveries, five patients had regional anesthaesia, with the remaining receiving other means of pain relief/anaesthesia. The average estimated postpartum blood loss in all pregnancies was 479 ml.

Management of heparin skin allergies can include topical steroids and antihistamines and considering switching between the different LMWHs. However, as LMWHs have similar pharmacological profiles, it is unlikely that switching between different types of LMWH may help in reduction of the skin allergy. More recently, fondaparinux has been observed to cause minimal skin reactions in comparison to LMWH.

Previous to our study, the largest cohort of patients analysed was a prospective study with 12 pregnancies, in which the authors reported no adverse effects to fondaparinux (Knol *et al*, 2010). Furthermore, case studies also report the safe use of fondaparinux in pregnancy (Rubin & Rubin, 2003; Efird & Kockler, 2006; Mazzolai *et al*, 2006; Wijesiriwardana *et al*, 2006; Ciurzynski *et al*, 2011). A study of the *in vivo* use of fondaparinux in five pregnant patients found clinically insignificant levels in cord blood, thereby concluding that the possible trans-placental transfer was minimal and is not associated with any increased risk of harm to the foetus (Dempfle, 2004). Therefore, it appears that fondaparinux may be a safe alternative anti-coagulant in the case of LMWH intolerance as there are no reported adverse complications to the mother or fetus during pregnancy, as seen in our cohort of patients and previous literature.

There are some limitations to this study in that only 15 pregnancies were included in the analysis. Nevertheless, this still represents the largest cohort of patients analysed to date. It is possible that tinzaparin, the LMWH of choice in our institution, may be associated with higher allergic reactions as was nadroparin in the reported study in comparison with other LMWHs (Schindewolf *et al*, 2013). Although the Royal College of Obstetricians and Gynecologists (RCOG) guidelines do recommend anti-Xa level monitoring specific to fondaparinux in high-risk cases where available

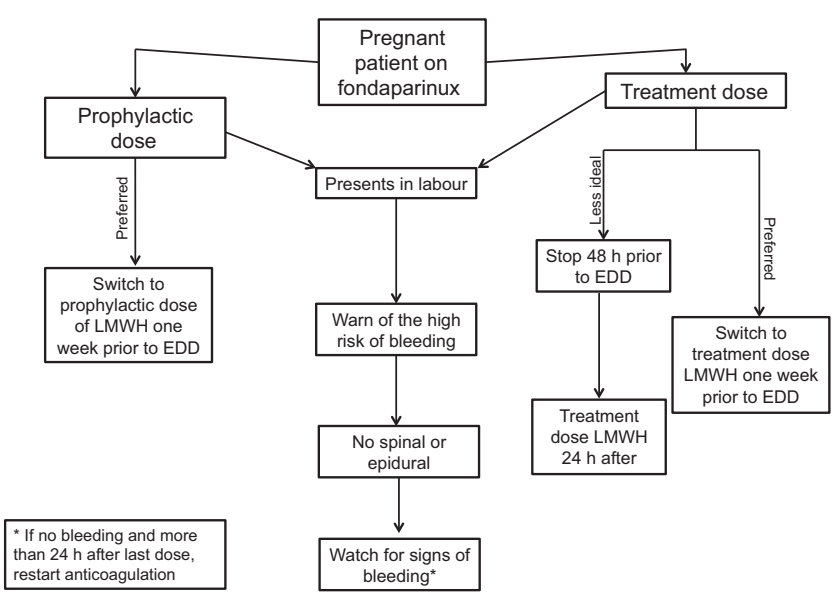

Fig 1. Algorithm for managing pregnant females receiving prophylactic or treatment-dose fondaprinux in preparation for delivery. The indication for using fondaparinux has to be allergy or intolerance to LMWHs and not heparin-induced thrombocytopaenia. Preferred suggests the safest option. LMWH, low molecular weight heparin; EDD, expected date of delivery.

(RCOG, 1995), we did not perform evaluate this parameter due to the lack of assay availability. Finally, no assessment of the cord blood fondaparinux levels was undertaken to determine the risk of fondaparinux crossing the placental barrier. However, there was no reported neonatal bleeding in this cohort.

Due to the lack of experience in using fondaparinux in pregnancy, it is imperative that physicians devise a delivery care plan ahead of the expected date of confinement in order to minimize complications (Fig 1).

In summary, fondaparinux has proven to be a safe and efficacious alternative anti-coagulant in women with heparin intolerance in pregnancy. Further larger, multicentre studies are required to understand the greater impact of fondaparinux on maternal and fetal well-being.

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Disclosure of interests

None.

Authorship contribution

E.E designed the study, collected the data and wrote the manuscript. J.T designed the study and wrote the manuscript. L.B designed the study and critically edited the manuscript. S.B collected the data. C.T, M.J.N, and C.R.M.H critically edited the manuscript. All authors approved the final version of the manuscript.

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Formal ethical approval was not required for this study.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table SI. Anti-coagulation regimen during pregnancy.
Table SII. Delivery and postpartum case details.

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