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Mini Review

Fondaparinux in pregnancy: Could it be a safe option? A review of the literature

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ABSTRACT

During pregnancy thrombo-prophylaxis could be required in high risk women. If a severe allergic reaction to low-molecular-weight-heparin (LMWH) or a heparin-induced-thrombocytopenia (HIT) occurs, it's mandatory to stop the drug. Fondaparinux could be an effective option. In the present review, the maternal and pregnancy outcomes of 65 pregnancies in women using Fondaparinux were reported. It was well-tolerated and rate of pregnancy complications was similar to that observed in general population. Regarding congenital malformations, further studies are necessary to investigate the safety of the drug.

Contents

Over the past few years, low-molecular-weight heparin (LMWH) has replaced unfractionated heparin as the agent of choice for the treatment and prevention of venous thromboembolism (VTE) during pregnancy because it has a better safety profile with respect to heparin-associated osteoporosis and heparin-induced thrombocytopenia (HIT), as well as reduced monitoring requirements [1]. However, adverse reactions to LMWH can occur *via* a type I hypersensitivity reaction (urticarial rash), skin necrosis due to vasculitis (type III reaction) or a heparin-induced-thrombocytopenia (HIT).

Fondaparinux sodium is a synthetic pentasaccharide that strongly binds to antithrombin and enhances the inactivation of factor Xa without interaction with factor II or platelets. Several studies showed that fondaparinux has an efficacy comparable to LMWH or UFH in the prevention of VTE in major orthopedic surgery, in the treatment of deep vein thrombosis (DVT) as well as pulmonary embolism (PE) without any increase of major bleeding [2]. Fondaparinux sodium has a very low cross-reactivity with both LMWH and UFH and few case reports describe reactions at the injection site of a single dose [3]. Rarely, anti PF4/heparin antibodies are generated during fondaparinux treatment, but they are not able to cause thrombocytopenia, because they do not bind PF4/fondaparinux complexes [4].

When heparin intolerance or HIT occurs in pregnant women who need thromboprophylaxis, there are limited alternative anticoagulant choices, fondaparinux could been suggested as an option.

Warfarin and hirudin cross the placenta and are associated with embryo and fetal toxicities. Lagrange et al. [5] did not observe placental transfer of fondaparinux in an *in vitro* model with the use of dually perfused human cotyledon. On the other hand, fondaparinux has been reported to pass *in vivo* the placental barrier, resulting in low but measurable anti–factor Xa activity in umbilical-cord blood, so that a potential hazard cannot be ruled out [6,7]. However, the use of fondaparinux in pregnant women is suggested by a level 2C recommendation from the American College of Chest Physicians for the treatment of those cases with severe allergic reactions to heparin (e.g. HIT) that cannot receive danaparoid [8].

Out of 68 pregnancies so far reported [6,7,9–16] (Table 1), three were considered not evaluable, because in two cases fondaparinux

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had been administered one and nine days before delivery [6], and in one case the pregnancy outcome had not been described [11]. Of the remaining 65 cases, none was associated with major bleeding. Pregnancy was complicated by recurrent VTE in one case (1,5%). In this woman, who weighed 99 kg and suffered from three previous VTE events, the initial dose of fondaparinux was 7,5 mg daily. Considering that the recommended dose is 10 mg for weight 100 kg, it could be considered that the recurrent DVT was due to inadequate anticoagulation, rather than treatment failure [15]. As the number of women receiving fondaparinux because of a history of previous DVT was 27, the failure rate for this indication was 3.7% (95% CI; 0.6%-18.3%).

Obstetric complications occurred in 18 cases (27,5%) with spontaneous abortions in 13 cases (20%) [12,15], ectopic pregnancy in one case (1,5%) [12], preterm rupture of membranes in one case (1.5%) [15], early preeclampsia in one case (1,5%) [11] and intrauterine fetal growth retardation in 2 cases (3%) [7,15]. (Table 1). Thirty-nine women were exposed to fondaparinux starting in the first trimester of pregnancy; of these, 31 had a history of previous fetal loss. The vast majority of miscarriages (12/13) occurred in women with a history of previous fetal losses; therefore, the rate of miscarriages in the women without previous fetal losses was 12,5%. Despite the fact that these women were at high risk for a poor pregnancy outcome, the rate of pregnancy complications reported is comparable to that observed in general population [19]. Notably, in one case, in which fondaparinux was started at the 7th week, pregnancy was interrupted because of fetal abnormalities (tetralogy of Fallot and Dandy-Walker syndrome) [15].

Almost all of women were prescribed fondaparinux for hypersensitivity to LMWH, but only one was reported to have cutaneous rash during administration of fondaparinux (1,5%) [12]. In the case reported by Buonomo et al. [16] allergy tests (skin prick and intradermal test) were performed also for testing fondaparinux tolerance.

Winger et al. [12] is the only study which analyzed the safety of fondaparinux versus a low molecular weight heparin (enoxaparin) therapy. In this retrospective study of women with a history of recurrent (≥3) miscarriages, and/or history of infertility with acquired or hereditary thrombophilia were started on anticoagulants on day 6 of the conception cycle and continued through at least 12 weeks of pregnancy. Patients also received low-dose-aspirin and other immunotherapies (immunoglobulin, tumor necrosis factor-alpha, corticosteroids, adalimumab or etanercept). The study demonstrated that fondaparinux was well-tolerated and no increase in birth defects, severe bleeding related complications, or serious allergic reactions were observed compared to enoxaparin therapy.

Although numbers are limited, the pooled efficacy of fondaparinux at preventing pregnancy-related VTE in this analysis is comparable to that seen in a prospective Swedish national study of obstetrical LMWH prophylaxis. The safety profile in the current analysis with respect to hemorrhagic events and hypersensitivity is satisfactory [17].

Table 1
Review on the use of Fondaparinux in pregnancy.

Study	Cases (no)	Indication for Thrombo-prophylaxis	Start of treatment (trimester)	Dose (mg)	Gestational age at delivery (weeks)	Birth Weight (g)	Outcomes (Efficacy/Safety)
Dempfle et al., 2004 [6]	5	Previous DVT(n = 1), thrombophilia (n = 4)	3rd (1–101 days before delivery)	2,5 OD	Not reported	Not reported	No VTE/no major bleeding/no adverse pregnancy outcome
Wijesiriwadana et al., 2005 [9]	1	Previous DVT during pregnancy	3rd through delivery	2,5 OD	39	3570	No VTE/ no major bleeding/no adverse pregnancy outcome
Mazzolai et al., 2006 [10]	1	Protein S deficiency and previous DVT	2nd (150 days before delivery)	2,5 OD	Not reported	Not reported	No VTE/no major bleeding/no adverse pregnancy outcome
Harenberg et al., 2007 [7]	1	Systemic lupus, recurrent VTE, previous pregnancy loss	Before pregnancy through delivery	2,5 + aspirin 100 mg OD	34	1240	No VTE/ no major bleeding /growth retardation
Gerhardt et al., 2007 [11]	1 [d]	Previous VTE	2nd through delivery	2,5 OD	39	Not reported	No VTE/no major bleeding/ early preeclampsia
Winger et al., 2009 [12]	29	Recurrent pregnancy loss and/or infertility with thrombophilia	Day 6 through at least 12 weeks of pregnancy	2,5 OD + aspirin 81 mg	37,3 ± 2,2 (mean ± SD)	2733 ± 753 (mean ± SD)	No VTE/ no major- bleeding / 11 pregnancy losses (38%)
Knol et al., 2010 [13]	12	Unprovoked VTE (n = 3), VTE during COC [c] (n = 7), recurrent pregnancy loss (n = 2),	1st (2 cases) 2nd (8 cases) 3rd (2 cases) through delivery	2,5 BID	Median 39 (range 33–42)	Median 3685 (range 1795–4330)	No VTE/no major bleeding/ no adverse pregnancy outcome
Ciurzynski et al., 2011 [14]	1	HIT[b] in a woman with pulmonary embolism during pregnancy	3rd	7,5 OD	37	2620	No VTE recurrence / no major bleeding/ no adverse pregnancy outcome
Elsaigh et al., 2014 [15]	15	Previous VTE (n = 11), DVT during pregnancy (n = 1), thrombophilia (n = 1), High BMI and family history of VTE (n = 1) recurrent fetal losses (n = 1),	1st (6cases) 2nd (8 cases) 3rd (1 case) through delivery	2,5 OD (n = 5) 5 mg OD (n = 1) 7,5 mg OD (n = 8) 10 mg OD (n = 1)	Median 39 (range 23–41)	Median 3330 (range 429–4050)	One recurrent DVT / No major bleeding / 2 foetal losses (1 premature rupture of membranes 1 growth retardation 1 termination due to foetal abnormalities)
Buonomo et al., in press [16]	1	Thrombocytemia previous PE, recurrent pregnancy loss	Positive pregnancy test through delivery	2,5 OD + aspirin 100 mg + interferon 2,5 MU three times per week	36	2280	No VTE [a]/ no bleeding/ no adverse pregnancy outcome

[a] Venous trombo-embolism;
[b] Heparin-induced thrombocytopenia,
[c] Combined oral contraceptive use.
[d] a second case was described from 13th to the 26th week only.

Despite these favorable reports on tolerability of fondaparinux in pregnancy, it should be again underlined that it can pass the placental barrier in vivo, resulting in measurable anti-factor Xa in umbilical cord blood. It is matter of concern that out of 65 pregnancies treated with fondaparinux, one was complicated by multiple congenital anomalies, with a rate of 1,5% (95% CI; 0.3%-8.2%). Comparison with the frequency observed in the general population (0.16%) is difficult, given the small number of cases included in our analysis [18]. Larger population studies are needed to establish the safety of the drug, in term of incidence of fetal malformations. However, this observation should mandate great caution in prescribing fondaparinux to pregnant women, limiting it to the management of HIT or to severe allergic reactions to LMWH (not responsive to a change in formulation), at least during the first trimester.

Fondaparinux 2,5 mg O.D. should be considered as a prophylaxis dose. The standard dose for the treatment of DVT or PE is 7.5 mg daily. This should be increased to 10 mg daily for body weight >100 kg and decreased to 5 mg daily for body weight <50 kg. Phase III studies demonstrated that at these doses both efficacy and safe profiles were similar to the comparator [20]. Whenever possible, fondaparinux should be stopped at least 24 hours before delivery and restarted 6 hours after delivery or 12 hours after removing the anesthetic neuroaxal catheter. Furthermore, we recommend to perform allergy test in case of type I or type IV hypersensitivity reactions to exclude cross-reactivity before any treatment with fondaparinux in order to avoid any unexpected reactions.

In conclusion, fetal safety is an important and crucial issue when considering a new anticoagulant therapy in pregnancy and an accurate evaluation of risks and benefits should always be performed and the results discussed with the patient. According to the available data, fondaparinux could be considered as an effective option in women requiring anticoagulation in presence of HIT or severe allergic reactions to heparin; nevertheless given limitations in the available data, caution is warranted during the first trimester.

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