Case Report

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Antithrombotic Prophylaxis with Fondaparinux in Two Pregnant Women with Previous Cerebral Vein Thrombosis

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Abstract

Fondaparinux, a subcutaneous synthetic pentasaccharide that selectively inhibit factor Xa, seems to be a safe and efficacious alternative to low molecular weight heparin in prevention and treatment of venous thromboembolism in pregnant women who had developed severe adverse reactions to heparin.

Two women with previous cerebral vein thrombosis received antithrombotic prophylaxis during pregnancy with fondaparinux 2.5 mg od because of previous hypersensitivity to low molecular weigh heparin. No thrombosis recurrence, maternal or fetal bleeding were observed, but both newborns were small for gestational age. Antithrombotic prophylaxis with fondaparinux was effective and safe in two pregnant women with previous cerebral vein thrombosis, but its potential side effects on fetal growth should be further elucidated.

Low molecular weight heparin (LMWH) is the drug of choice for the treatment and prevention of venous thromboembolism (VTE) in pregnancy [1]. Adverse reactions to LMWH, i.e., local skin reactions, systemic rash and heparin induced thrombocytopenia (HIT) may occur and impose LMWH discontinuation and its avoidance thereafter [1]. Fondaparinux, a subcutaneous synthetic pentasaccharide that selectively inhibit factor Xa, seems to be a valid alternative to LMWH for both treatment and prophylaxis of VTE also during pregnancy [1], but data are limited to case reports or case series [2-8]. We report on the successful use of antithrombotic prophylaxis with fondaparinux in two pregnant women with previous cerebral vein thrombosis who had developed HIT (case 1) and severe skin reaction (case 2) during LMWH treatment.

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Case 1

A 33-year-old woman became pregnant for the first time in 2012. At the age of 20 years she developed a cerebral vein thrombosis during oral contraceptive use. After 5 days of therapeutic subcutaneous calcium heparin she developed a severe HIT (platelet count 40 x 10^3/mmc) and a right iliac vein thrombosis. She shifted to a vitamin K antagonist (warfarin) that continued for 18 months. Thrombophilia screening was normal. At the beginning of pregnancy she weighted 56 kg (BMI 18.9 kg/m^2). Fondaparinux 2.5 mg od s.c. was started at the 5th gestational week and continued during pregnancy and 6-weeks puerperium. She delivered spontaneously at the 38th gestational week a male newborn of 2550 g (APGAR 10 at 5 and 10 min). Her weight was 64 kg (BMI 21.6 kg/m^2). Anti-factor Xa activity measured at the 15th, 20th and 36th gestational week was 0.12 UI/ml, 0.11 UI/ml and 0.12 UI/ml, respectively (desired range 0.2-0.6 UI/ml).

Case 2

A 26-year-old woman became pregnant for the second time in 2009. In 2000, at the age of 17 years, she developed a cerebral vein thrombosis during oral contraceptive use, treated with therapeutic dose of LMWH and subsequently warfarin for one year. Thrombophilia screening was normal. Her first

pregnancy was in 2005, and antithrombotic prophylaxis with LMHW (calcium nadroparin 3800 IU od during pregnancy and puerperium) was given. At the beginning of her pregnancy she weighted 55 Kg (BMI 19 kg/m^2). She spontaneously delivered at the 37th gestational week and 5 days a male newborn of 3040 g (APGAR 10 at 5 and 10 min). Her weight was 73 kg (BMI 25.3 kg/m^2). No adverse events were observed with LMWH prophylasis. When she become pregnant for the second time her weight was 58 Kg (BMI 20.1 kg/m^2). She started calcium nadroparin 3800 IU od at the 4th gestational week, but at the 9th week she developed a diffuse systemic skin reaction with abdominal rush. She was therefore switched to sodium enoxaparin 4000 UI od but the skin reaction worsened in few days, and wide urticarioid papulae appeared around the site of subcutaneous injections and diffuse itch. Hence, at the 10th gestational week enoxaparin prophylaxis was stopped and fondaparinux 2.5 mg od s.c. was started. She spontaneously delivered at the 37th gestational week a female newborn of 1950 g (APGAR 10 at 5 and 10 min). Her weight was 76 Kg (BMI 26.3 kg/m^2). Anti-factor Xa activity was not measured.

In both patients fondaparinux prophylaxis was stopped 12 hours before and restarted 12 hours after delivery and continued for the whole 6 weeks period of the puerperium. Epidural labour analgesia and neuroaxial blockade at delivery was avoided because of the long half-life of fondaparinux (13-21 hours) [9]. Both women decided to breast feed, although discouraged by us because of the lack of data on fondaparinux excretion in human milk. No adverse effects were observed in the newborns over 6 months lactation. Platelet count remained normal during all pregnancy and puerperium and no skin reactions, bleeding or recurrent thrombosis were observed.

Discussion

To date, the use of fondaparinux during pregnancy has been reported in few case reports [2-6] and two small cases series [7,8]. The first case series reports the use of fondaparinux 2.5 mg bid in 10 women (12 pregnancies) with previous hypersensivity skin reaction to LMWH and no pregnancy, maternal of fetal complications were observed. In the second case series a prophylactic dose of fondaparinux 2.5 or 5 mg od was used for the same indication in 6 women and a therapeutic dose of 7.5 or 10 mg od in other 9 women with previous hypersensivity skin reaction to LMWH. Ten pregnancies (3 with prophylactic and 7 with therapeutic dose) were uncomplicated and resulted in healthy newborns. Two pregnancies resulted in early miscarriage and one twin pregnancy ended with premature spontaneous rupture of membranes at the 22nd gestational week. One pregnancy ended for a willingly termination due to fetal cardiac malformations and one woman delivered at the 37th week with caesarean section a small for gestational age (SGA) newborn of 2268 g with cerebral palsy. One additional woman had recurrent deep vein thrombosis during fondaparinux therapy with 7.5 mg od. A retrospective study of 127 pregnancies without prior VTE but infertility or pregnancy loss who received fondaparinux 2.5 mg od (n=29) or enoxaparin 3000 UI bid (n=98) until at least 12 weeks of pregnancy showed no maternal or fetal adverse events [10].

Recommendations on the use of fondaparinux in pregnant women are based on such limited literature and are restricted to selected women who developed intolerance to LMWH, whereas an alternative anticoagulant treatment is recommended for breast feeding women (grade 1C) [1], given the paucity of information on breast milk transfer. Fondaparinux has a low potential to induce cutaneous reactions [11], however skin prick and intradermal testing may be useful in selected patients [12]. No data are available about the human reproductive risk of the new oral direct anticoagulant drugs, i.e. dabigatran, rivaroxaban and apixaban, but their use is not recommended because of animal reproductive toxicity [1].

This is the first description of use of antithrombotic prophylaxis with fondaparinux during pregnancy in two women with prior cerebral vein thrombosis. Both pregnancies had a normal course, and spontaneous vaginal delivery occurred at term. No skin reactions, bleeding, platelets reduction or recurrent thrombosis was observed. However, both newborns were SGA, with a birth weight below the 10th percentile. In particular, the newborn n. 2 presented a severe fetal growth restriction with also a percentile reduction from the growth curve of the abdomen circumference of more than 40% by ultrasound. Controversial data are reported on pentasaccharide exposure in utero. No placental transfer of fondaparinux was observed in a human cotyledon model (small lobe on the uterine or maternal surface of maternal plasma), but anti-factor Xa activity was detected in the umbilical cord plasma in a small series of mothers treated with prophylactic doses of fondaparinux [13,14]. Although the anti-factor-Xa activity was very low (approximately 1/10 the maternal activity) a potential harmful effect of fondaparinux on the fetus can not be excluded. Unfortunately, anti-Xa activity was not measured in blood cord and in maternal milk in our two women and therefore the placental and milk transfer could not be evaluated. We only measured the anti-Xa activity in case 1 woman, that was below the desired range confirming that anti-factor-Xa activity monitoring is not warranted with prophylactic doses of heparin. Both women underwent an extensive thrombophilia screening (antithrombin-, protein C- and protein S-deficiency, factor V Leiden and prothrombin G20210A mutations, hyperhomocysteinemia and factor VIII levels) including the search of antiphospholipid antibodies (lupus anticoagulant, antcardiolipin and anti-b2 glycoprotein I antibodies IgG and IgM), and tested negative. Hence, known thrombophilia abnormalities can not be responsible nor for the cerebral vein thrombosis nor for the fetal growth restriction [15], although still unknown abnormalities may be implicated in both events.

In conclusion, we describe the effective and safe use of prophylactic doses of fondaparinux in two pregnant women with previous cerebral vein thrombosis. We underline that both newborns were SGA, although no plausible relationship with an eventual anticoagulant effect on the embryo and the fetus can be surmised. Further data on pregnancy outcome in women treated with fondaparinux are warranted. Fondaparinux use in pregnancy should be limited to women with severe allergic reaction to heparin or previous HIT.

Contribution to authorship

SMP was the first to have the idea to perform the study and wrote the first draft; FG obtained information of the women; IM was involved in the conception of the study and contributed to the final manuscript. All contributed to the revision of the manuscript.

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