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

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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.

Keywords

Anticoagulants, pregnancy, direct oral anticoagulants, heavy menstrual bleeding, Rivaroxaban

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Introduction

Direct oral anticoagulants (DOACs, or non-vitamin K oral anticoagulants (NOACs)), as the name suggests, are oral anticoagulants with a direct inhibitory action, either against factor X or factor II (thrombin). Since 2012, a number of these agents have been licensed for use for a range of indications including thromboprophylaxis following orthopaedic surgery, stroke prevention in patients with atrial fibrillation and treatment and prevention of venous thrombo-embolism (VTE). They include rivaroxaban, apixaban, edoxaban and dabigatran.

As DOACs have a favourable profile for safety and efficacy compared to warfarin, the use of the all-oral regimes are increasingly used across the United Kingdom as first-line treatment for deep vein thrombosis and pulmonary embolism. DOACs have many of the attributes of the ideal anticoagulant: they are as effective as warfarin in treating and preventing deep vein thrombosis and pulmonary embolism, with improved safety record, in particular, reduced risk of intracranial bleeding. Unlike warfarin which often takes a week to reach therapeutic levels, these directly acting agents reach peak activity within the first couple of hours following ingestion. They do not require monitoring as they have predictable pharmacokinetics and few drug interactions. Two of the agents, Rivaroxaban and Apixaban, have simple all-oral treatment protocols for management of VTE patients. Edoxaban and Dabigatran require the use of low molecular weight heparin (LMWH) for 5 days lead-in before starting these DOACs. For this reason, these two agents are less likely to be popular for VTE management.

Rivaroxaban is the more widely used, as this drug was first to market for VTE use. As the age range for VTE is much wider than that for AF or orthopaedic operations, there is increasing use in younger individuals for VTE treatment and secondary thromboprophylaxis. As a result, many women of child-bearing age may now receive treatment with these agents. Obstetricians and gynaecologists may be unfamiliar with these newer oral anticoagulants and their potential effects, and this case report highlights the need for those specialising in Obstetrics and Gynaecology to be aware of the significant potential problems that may occur with these agents.

Case report

A 20-year-old woman was referred to the Obstetric and Gynaecology (O&G) clinic by her General Practitioner for consideration of termination of an unplanned pregnancy, conceived whilst on Rivaroxaban.

She had previously suffered a massive pulmonary embolus aged 18 years. Risk factors for her VTE at that time were, being on the combined oral contraceptive pill, and having a family history of a pregnancy-associated VTE. She had been treated with warfarin initially, but due to poor time in therapeutic range this was changed to Rivaroxaban 20 mg daily. She took a progestosterone-only pill (desogestrel) for contraception. Review at the O&G clinic revealed that since being on Rivaroxaban, she had suffered ongoing vaginal bleeding between menstrual periods in addition to heavy menstrual bleeding. Ultrasound scan unexpectedly demonstrated a fetus of 25+ weeks' gestation. Rivaroxaban was discontinued and low molecular weight heparin substituted, at a dose of 120 mg daily. This dose was chosen as a high intermediate dose in view of the previous history of a life-threatening thrombosis which was pill-associated. Regular follow-up with fetal scans at 28 and 34 weeks showed normal growth and no identifiable fetal abnormality or bleeding. An echocardiogram showed no evidence of right heart strain. A multidisciplinary approach to delivery plan was adopted, with review by an anaesthetist, obstetrician and haematologist. The plan for delivery included: reduction of the enoxaparin dose at 38 weeks' gestation, and to omit this at onset of labour; regular assessment of the cervix for rupture of membranes when favourable to gain some control over delivery.

However, our patient continued on the same dose until she presented at 39+6 weeks' gestation with spontaneous rupture of membranes. Despite syntocinon, there was poor progression over the next 24 hours, and due to the development of a pathological CTG, and length of time off anticoagulation, an emergency Caesarean section was performed. A morphologically normal male baby of average weight (3.35 kg) was delivered. There was no evidence of intracranial haemorrhage on cranial ultrasound scan. Follow-up routine examinations were normal.

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Discussion

To date, there has been only one previous case report of a pregnancy conceived whilst on Rivaroxaban;¹ this was not, however, reported in an obstetric journal. The diagnosis was made at 19 weeks' gestation and resulted in a small for dates, morphologically normal male infant. The low weight was attributable to maternal smoking in that case. There are no reported similar cases with Apixaban or Dabigatran up to the present time.

Pregnant women were excluded from participating in all the large trials of the DOACs. However, 10 patients became pregnant during the Edoxaban study,² with exposure occurring in the first trimester and lasting about 6 weeks. There were six live births (two pre-term), one first trimester spontaneous abortion and three elective pregnancy terminations.

The summary of product characteristics (SPC) documentation for all the DOACs advise against use in pregnancy and breast feeding. Rivaroxaban, Dabigatran and Edoxaban are category C listed by US FDA (which states – *animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks*).

Toxic effects of Rivaroxaban during pregnancy have been demonstrated in animal studies (rats and rabbits), including post-implantation loss, abnormal ossification, liver abnormalities, increased incidence of common malformations and placental changes. These effects were observed at 'clinically relevant plasma concentrations' of Rivaroxaban.^{3,4} The observations are similar to those noted with vitamin K antagonists. The Dabigatran SPC⁵ describes decreased implantation and pre-implantation loss at 5–10× exposure level in patients. At the same dose, it decreased fetal body weight and viability, caused increased vaginal and uterine bleeding. Although Dabigatran increased the incidence of delayed or irregular ossification of fetal skull bones and vertebrae in rats, it did not induce major malformations in rats or rabbits. In animal reproduction studies in Edoxaban,² rabbits showed increased incidence of gall bladder variations at 65× maximum recommended human dose (MRHD), increased post-implantation pregnancy losses at 49× MRHD in rats and ×65 in rabbits.

Interestingly, Apixaban is classified as category B, as animal studies did not indicate direct or indirect harmful effects with respect to reproductive toxicity.⁶ Increased incidence of maternal bleeding was observed in mice, rats and rabbits at maternal exposures that were 19×, 4× and 1× MRHD. No maternal or fetal deaths were attributable to bleeding, and no evidence of increased risk of fetal malformations or toxicity. The UK and Australian recommendation is 'use is not recommended', whilst the US recommendation is that this drug should be used in pregnancy only if the benefits outweigh the risk to the mother and fetus.

The mechanism of toxic fetal effects is unknown, but is likely to be similar to that of warfarin and other vitamin K anticoagulants, since not only are these effects comparable, but also the final common pathway is via an effect on one or more coagulation factors (Factors II, VII, IX and X for vitamin K antagonists, Factor Xa for Rivaroxaban, Apixaban and Edoxaban, and Factor IIa for Dabigatran). There are other side-effects common to all the anticoagulants outside pregnancy, such as gastro-intestinal disturbance.

The Royal College of Obstetricians & Gynaecologists' (RCOG) recent guidelines in April 2015 states 'Non-vitamin K anticoagulants should be avoided in pregnancy, and use of NOACs is not recommended in women who are breast feeding'.⁷ Similarly, ACCP guidelines (2012) warns not to use in pregnancy or breast feeding.⁸

Our patient had menorrhagia and intermenstrual bleeding. Heavy menstrual bleeding (HMB) is emerging as a significant problem with Rivaroxaban, with two recent publications documenting the issue.^{9,10} As yet it is not known whether this is a class effect or due to the particular dosing schedule for Rivaroxaban. However, as a group the DOACs are increasing in number and use and it is important that those women referred to an O&G clinic on these agents are recognised and counselled appropriately.

In addition, the difficulty with ongoing bleeding masked early diagnosis of pregnancy in our patient. Our case demonstrates the need to emphasise the need for robust measures for contraception whilst on a DOAC. Our patient was on a progesterone only preparation when she conceived. Although HMB may be a particular issue with Rivaroxaban, women of reproductive age may experience heavy and prolonged menstrual bleeding whilst on any anticoagulant therapy and should also be assessed for menstrual disorders to ensure that prompt and appropriate treatment is instituted. In the paper by Ferreira et al.,⁹ 12 of 15 women of Afro-Caribbean ethnic origin had evidence of uterine fibroid disease. Women should be assessed for:

1. Degree of menstrual difficulties – objective evidence of HMB, symptoms of anaemia.
2. Anticoagulant medication adherence – women may decrease dosage of anticoagulation to reduce menstrual flow, risking recurrence of thrombosis. Also, a change of anticoagulant may help in some cases.
3. Appropriate contraceptive choice, and the need to emphasise strict adherence if on an oral preparation. Alternative routes may be more robust to prevent unplanned pregnancies, such as levonorgestrel-releasing IUD (Mirena); depot preparations of progestogen-only medication (depot medroxyprogesterone acetate); etonogestrel implant (implanon) or barrier methods. Progestin-only preparations may be preferable to oestrogen-containing preparations in patients at increased thrombotic risk, although it is likely that the anticoagulation will be sufficient to off-set this risk. Advice about appropriate contraception should be part of the medical care provided for these women.^{11,12}
4. Structural abnormalities that may be contributing to HMB, such as uterine fibroids. Pelvic imaging should be requested based on history and examination.

In conclusion, there is a clear need for Obstetricians and Gynaecologists to be aware of the rapidly increasing use of these agents, and their potential problems. Women of child-bearing age should be specifically counselled that DOACs are contra-indicated in pregnancy, counselled carefully about suitable contraception, and that in the case of excessive menstrual bleeding or inter-menstrual bleeding, in addition to investigating for gynaecological disorders, alternative anticoagulation should be considered.

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