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Anticoagulation in Pregnancy and Post-partum: New Options

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Abstract

The ideal anticoagulant in pregnancy and postpartum is yet to be found. Vitamin K antagonists are cumbersome to use - having multiple interactions with food and other drugs, requiring frequent laboratory monitoring and necessitating switch over to heparin in early pregnancy and around delivery. Direct Oral Anticoagulants (DOAC) are now therapeutic alternatives to Warfarin in the management of venous thromboembolism, non-valvular atrial fibrillation, and acute coronary syndromes. Their use in pregnancy and the postpartum period is to be explored. Our case is a 35-year, third gravida with two living issues with Rheumatic heart disease (severe mitral and tricuspid regurgitation, moderate pulmonary artery hypertension and chronic atrial fibrillation). She presented at 18 weeks' gestation with active bleeding from a low-lying placenta. This being an unwanted pregnancy, she underwent hysterotomy with bilateral tubal ligation. Post procedure, warfarin was initiated in view of her chronic atrial fibrillation, and slowly titrated to a target an INR of 2-3. She developed spontaneous haemoperitoneum on warfarin therapy, which was conservatively managed. After resolution of haemoperitoneum, attempting to establish adequate anticoagulation on heparin and warfarin prolonged her hospital stay by an additional 3 weeks of hospital stay until dabigatran was initiated and the patient could be discharged. DOACs offer several advantages - efficacy, safety, predictable pharmacokinetics. Although category C drugs in pregnancy, as data accumulates on exposures of these drugs in pregnancy, they may be a future therapeutic option which avoids many of the problems associated with current anticoagulation regimes.

Keywords: ***Cardiac disease in pregnancy; Anticoagulation; Dabigatran; Critical care obstetrics; Rheumatic heart disease***

1. Introduction

Pregnancy affects all components of Virchow's triad: a hypercoagulable state, with raised clotting factors; stasis (due to compression of pelvic veins and inferior vena cava by the gravid uterus); and endothelial injury, as a result of this stasis. Women

who have had a thrombotic event, those with thrombophilia or APLA syndromes or those with cardiac disease (mechanical heart valves or atrial fibrillation) require safe and effective anti-coagulation prior to conception, during pregnancy and in the peuperium. The ideal anti-coagulant should have a rapid onset of action, preferably be oral and have stable pharmacodynamic and pharmacokinetic properties, resulting in less interaction with food and other drugs and less need for constant monitoring. However, all currently used anticoagulants remain less than ideal. The search for novel anticoagulants is still going on.

2. Case Presentation

Our patient is a 35-year resident of rural Bihar, third gravida with two living issues. A known case of rheumatic heart disease, she underwent mitral valve repair 10 years earlier but had residual severe mitral and tricuspid regurgitation, moderate pulmonary artery hypertension and chronic atrial fibrillation. She presented at 18 weeks' gestation with active bleeding from a placenta covering the cervical os. This being an unwanted pregnancy, the patient and her partner chose termination, and she underwent hysterotomy with bilateral tubal ligation. The procedure was uneventful. In the post-operative period, she was started on warfarin and low molecular weight heparin (as bridge therapy) to treat her chronic atrial fibrillation. The dose of warfarin was increased until at 4 mg once daily, the patient was adequately anticoagulated (INR - 2.4). Subsequently however, the patient developed haemoperitoneum spontaneously one week after surgery on the same dose of warfarin (INR 10.8).

The haemoperitoneum was managed conservatively by transfusing FFP to replace clotting factors and placing a pigtail catheter for drainage. Yet, after resolution of the haemoperitoneum, the problem of an appropriate anti-coagulation therapy persisted. The patient was restarted on intravenous unfractionated heparin and tablet warfarin. The dose of warfarin was slowly titrated upwards, but even at dose of 5 mg once daily, the INR remained inadequate (1.28), despite having bled at a lower dose. At this point, the patient was switched to dabigatran 150 mg twice daily, which solved many of the problems faced by the treating physicians: dabigatran had a fixed dose, unlike warfarin which requires titration to an adequate INR, which was dangerous in this patient who had bled at a lower dose. Dabigatran also, although as efficacious as warfarin, does not have as many interactions with food and other drugs and does not require laboratory monitoring, which is convenient to our patient from rural settings.

Our patient was discharged and followed up on an outpatient basis two weeks later. She was doing well with no complaints and no bleeding events.

3. Discussion

Our patient, post-hysterotomy with cardiac disease, after almost 6 weeks of unsuccessful anticoagulation with warfarin responded well to dabigatran therapy.

Warfarin is an effective drug for anticoagulation in pregnancy with cardiac disease or thromboembolism. It has the lowest risk of valve thrombosis (0-4% versus 9%-33% with unfractionated heparin and 5.8%-7.4% with low molecular weight heparin) [1]. However, there is an increased risk of miscarriages (28.6%) and embryopathy (0.6%-10%) with first trimester use, which is dose dependent. Therefore, for those on >5mg/day warfarin or >3mg/day phenprocoumon or >2mg/day acencoumarol, it is recommended to switch to heparin from 6-12 weeks gestation, which does not cross the placenta. Although there is a high risk

of foetal wastage even with this regime (22.7%). Moreover, this transition period has the greatest risk of thromboembolic complication in pregnant women with mechanical heart valves, possibly due to subtherapeutic levels of anticoagulation.

Novel oral anticoagulants (Factor Xa Inhibitors: Rivaroxiban, Edoxaban and Apixaban; and Direct Thrombin Inhibitors: Dabigatran), on the other hands, have distinct advantages. These drugs have a rapid onset of action, do not inhibit Cytochrome P450, have a predictable dose response and do not require routine coagulation monitoring or a bridging anticoagulation (heparin). It is currently licenced for the prevention of stroke and systemic embolism in patients with atrial fibrillation (in the absence of mechanical valves) and for treatment/prevention of deep vein thrombosis and pulmonary embolism. The RE-LY trial conducted on patients with atrial fibrillation demonstrated that dabigatran was as efficacious an anticoagulant as warfarin with similar or lower risk of bleeding [2]. The role of these agents in valvular heart disease in being investigated as well.

As Novel Oral Anticoagulants (NOACs) replace warfarin in clinical practice due to efficacy, safety and convenience, their use in women of reproductive potential also expands. Data on the use of NOACs in pregnancy is scarce. These are small molecules which in vitro studies have shown to cross the placenta, but the clinical risk of embryopathy is unknown. A review of 137 pregnancies with NOAC exposure (dabigatran, rivaroxiban, apixaban, edoxaban,) by Beyer-Westendorf et al [3], revealed 3 anatomical abnormalities that could be drug-related embryopathy (although with no recurring pattern). Animal models demonstrated secretion of some NOACs into breast milk. The International Society on Thrombosis and Haemostasis recommends that NOACs should be stopped immediately after confirmation of pregnancy and replaced by LMWH which does not cross the placenta. However, NOAC exposure does not warrant termination of pregnancy [4].

A systemic investigation on the effects of DOAC exposure in pregnancy may not be possible due to ethical and medicolegal considerations, but there is a need to establish registries which detail such exposures and collect data on the safety of such medication. This will help us find new alternatives to the conundrum of anti-coagulation in pregnancy and post-partum.

4. Disclosures

None

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