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Case Report

Low-dose warfarin therapy leading to embryopathy: a case report

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ABSTRACT

The development of specific dysmorphic features known as warfarin embryopathy or fetal warfarin syndrome is more likely to occur in fetuses exposed to maternal consumption of warfarin. Nasal hypoplasia and stippling of the vertebrae or bony epiphysis are the most consistent characteristics. Anticoagulation in pregnant patients might be difficult to manage. According to current recommendations, heparin or low-dose warfarin (≤5 mg/day) should be used. We report the case of a pregnancy where the mother was anticoagulated with low-dose warfarin due to a mechanical mitral valve. Warfarin was required at a dose of 3 and 4 mg on alternate days and was switched to heparin from 10+4 weeks to 12 weeks. Nevertheless, the fetus presented with the signs of warfarin embryopathy. Through this report, we emphasize the need for optimising the choice and dosage of anticoagulants during pregnancy so as to provide the best maternal and fetal outcome.

Keywords: Anticoagulants, Fetal warfarin syndrome, Warfarin, Embryopathy

INTRODUCTION

Warfarin, a coumarin anticoagulant, works by inhibiting vitamin K epoxide reductase, which in turn suppresses the production of vitamin K-dependent coagulation factors (factors II, VII, IX, and X). For more than 50 years, it has been used in clinical settings. Because warfarin crosses the placenta, using it during pregnancy can result in spontaneous abortion, stillbirth, neonatal death, and premature delivery, as well as a number of congenital abnormalities such as fetal warfarin syndrome (FWS), warfarin embryopathy, or Di Sala syndrome.[1,2] Stippling of the vertebrae or bony epiphysis and nasal hypoplasia are the most common prenatal abnormalities. Other reported anomalies linked with FWS include congenital heart defects including atrial septal defect and patent ductus arteriosus (PDA), upper airway obstruction, choanal atresia, laryngeal abnormalities, short neck, telebrachydactyly, growth retardation, pectus carinatum, diaphragmatic hernia, optic atrophy, blind ness, deafness, microcephaly, hydrocephalus, agenesis of corpus callosum, Dandy Walker malformation, seizure, and mental retardation. It has been found in 15–25% of fetuses that were exposed to warfarin during the first trimester of pregnancy.[1,2] The 6th to 12th weeks of pregnancy are the most vulnerable.[3,4] The most severe and common side effects seem to occur at doses higher than 5 mg/day, suggesting that the impact is dose-dependent.[5]

There are serious risks for both the mother and the fetus when a woman with a mechanical heart valve becomes pregnant. To avoid thromboembolic consequences (TEC), all women with mechanical heart valves need therapeutic anticoagulation. Heparin-unfractionated heparin (UFH) or low molecular weight heparin (LMWH) and vitamin K antagonists (like warfarin) are the available options for anticoagulation. While warfarin use during pregnancy can result in FWS, it is the safest option in terms of maternal mortality and TEC.[6,7] Because of the low risk of fetopathy (<3%) and the mother's safety profile, the European Society of Cardiology (ESC) and the American Heart Association/American College of Cardiology (AHA/ACC) recommend that if the dose of warfarin is less than 5 mg per day, it should be continued throughout pregnancy.[8,9] The ESC guidelines additionally specify that

in these patients, stopping warfarin and switching to UFH or LMWH between weeks 6 and 12 may be taken into consideration. When the dose is greater than 5 mg/day, the ESC guidelines recommend stopping warfarin between 6 and 12 weeks and switching to either UFH adjusted based on activated partial thromboplastin time (aPTT) (target ≥2 times the control) or LMWH twice daily adjusted based on weight and anti-Xa levels. In contrast, the AHA/ACC guidelines recommend switching to LMWH twice daily during the prenatal period.[8,9] It is important to discuss with parents the available options and maternal and fetal risks associated with each regimen.

CASE REPORT

A 26-year-old primigravida attended the antenatal clinic at 10 weeks' gestation. She had rheumatic heart disease for 15 years of age and had undergone mitral valve replacement with posterior mitral leaflet and chordal preservation at the age of 20 years. In the present pregnancy, her cardiac functional status was class I according to the New York Heart Association criteria. She was taking oral warfarin sodium 3 and 4 mg alternate day and oral aspirin 150 mg/day. Ultrasound showed a single live intrauterine fetus corresponding to 10 weeks and 4 days. Given known teratogenic effects, the patient was given the option to switch to unfractionated heparin (1050 IU/hour) via continuous infusion preceded by a loading dose of 5000 IU after informed discussion with the patient. Genetics counselling was done and a cardiology opinion was sought. Heparin was continued till 12 weeks, after which warfarin was resumed to maintain international normalized ratio (INR) between 2.5 and 3.5.

An anomaly scan was done at 18 weeks of gestation, which showed premature ossification of the proximal and distal epiphysis of the left femur with stippling of the epiphysis of the coccyx, along with echogenic intracardiac foci. The fetal nose was normal. Warfarin embryopathy was diagnosed. After interdisciplinary counselling, the patient opted for the termination of pregnancy. She was admitted for bridging over to unfractionated heparin to maintain aPTT >2 times of control, followed by medical termination of pregnancy. She expelled a male fetus of 316 grams (Figure 1). Post-termination infantogram and autopsy could not be done as the patient refused any examination of the fetus due to religious reasons. Following the expulsion, the patient was started on unfractionated heparin and completely switched to warfarin 3 and 4 mg alternate day on day 3 to maintain INR between 2.5 and 3.5.

DISCUSSION

The first reports of a connection between warfarin consumption and congenital malformations in infants date back to the 1960s.[10,11] Franco et al proposed that warfarin may inhibit the activity of the arylsulfatase enzyme, which causes X-linked recessive chondrodysplasia punctata, which is phenotypically similar to warfarin embryopathy.[12] There are many reports of embryopathy and fetal loss occurring at a warfarin dose above 5 mg.[13] A recent meta-analysis of 494 pregnancies in 11 studies revealed warfarin embryopathy in 0.9% (0.4–2.4%) and fetal losses in 13.4% (8.4–24.7%).[14]

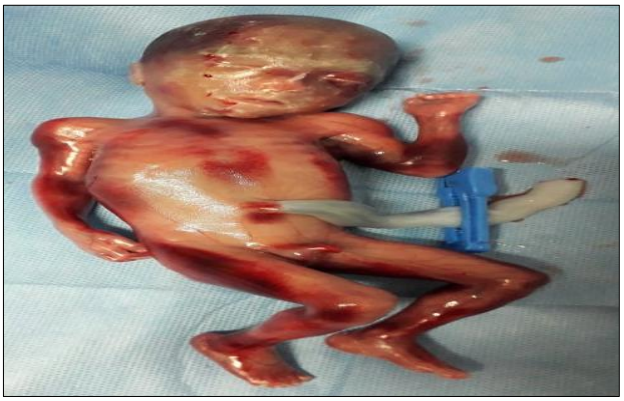

Figure 1: Photograph of expelled fetus.

While low doses of warfarin during the first trimester are associated with a lower risk of warfarin-related fetopathy, the risk of embryopathy is still present. Some studies indicate that risk is lower with lower doses, while others show that risk stays the same.[11,15,16] There are some examples in the literature of cases as the one we report, with a fetus presenting with features of FWS despite low doses of warfarin.[17-19]

In the case we present, current guidelines for anticoagulation during pregnancy were followed with the use of low-dose warfarin. There were no thromboembolic complications during pregnancy but the fetus presented with skeletal abnormalities typical of FWS.

CONCLUSION

In conclusion, RHD is still widespread among young people in developing nations like India. Many of them get mechanical replacement heart valves, followed by long-term oral anticoagulation with warfarin. It is important to have a prenatal conversation at an appropriate age about marriage, family planning, contraceptive services, and potential pregnancy difficulties. We emphasize that in order for the expectant mother to make an informed decision, the obstetrician and the caring cardiologist must have an objective conversation about the benefits and drawbacks of various thromboprophylaxis choices. It is also true that, as a developing nation, LMWH or UFH therapy during pregnancy could not be a viable or sustainable option due to its high cost.

Pregnancy is a prothrombotic state that raises the risk of maternal TEC, making it challenging to choose an anticoagulant to prevent TEC in pregnant women with mechanical prosthetic heart valves. The optimal anticoagulant strategy for pregnant women with a mechanical prosthetic valve is not universally agreed

upon. As a result, it is crucial to carefully assess the risks to both the mother and the fetus while discussing the various anticoagulation alternatives accessible to parents during pregnancy.

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