BMJ Case Reports

Rare disease

Fetal warfarin syndrome

Luke D Starling,[1] Ashutosh Sinha,[2] Duncan Boyd,[3] Anke Furck[2]

[1]Department of Paediatric Cardiology, Royal Brompton & Harefield NHS Trust, London, UK
[2]Paediatric Intensive Care Unit, Royal Brompton & Harefield NHS Trust, London, UK
[3]Neonatal Intensive Care Unit, Queen Charlotte's & Chelsea Hospital, London, UK

Correspondence to Dr Luke David Starling, l.starling@rbht.nhs.uk

Summary

A case of a baby born preterm with an antenatal diagnosis of aortic coarctation for which prostin was electively started at birth. The baby was found to be profoundly anaemic with no clear obstetric cause. Features consistent with antenatal intracerebral haemorrhage were noted on cranial ultrasonography in the context of severe coagulopathy, prompting investigations which confirmed fetal–maternal haemorrhage. It transpired that, following aortic and mitral valve replacements, the mother was anticoagulated with warfarin at conception, having misunderstood her cardiologist's advice that: 'you cannot get pregnant whilst on warfarin'. Following conversion to low molecular weight heparin, she suffered a stroke, thus warfarin was restarted, with an international normalised ratio of 3–4.7 during pregnancy. Following transfer to the paediatric intensive care unit, fetal warfarin syndrome was diagnosed. The coagulopathy and anaemia were corrected and aortic coarctation was excluded. The baby returned to the neonatal intensive care unit for ongoing care and was discharged home in good condition around his due date. At the present time, there is no clinically overt neurological deficit.

BACKGROUND

Warfarin is a common medication, and coagulopathy and anaemia (albeit less profound) are not infrequently encountered neonatal problems. This case highlights the existence of an uncommon neonatal clinical phenomenon —uncommon because warfarin is generally avoided in pregnancy (this case highlights why)—and emphasises the importance of clear communication between physician and patient, and potential consequences when information is misunderstood.

In addition, this case of fetal warfarin syndrome is phenotypically unusual in view of apparently isolated coagulopathy, manifesting fetal-maternal haemorrhage, in the absence of the more frequently reported clinical sequelae of warfarin embryopathy. This case also reminds us to ensure treatment of the whole patient, as acute problems can often be overlooked when another concern, particularly one such as congenital heart disease, predominates.

CASE PRESENTATION

A baby with an antenatal diagnosis of aortic coarctation and ventricular septal defect was born prematurely (34+6/40) at a tertiary central London teaching hospital. He was delivered by EmLSCS for reduced fetal movements and suspicious cardiotocograph, and born in poor condition requiring mask ventilation prior to transfer to the neonatal intensive care unit (NICU).

On NICU admission, the baby was haemodynamically unstable with preductal and postductal hypotension and metabolic acidosis with hyperlactataemia. At umbilical catheterisation, prolonged oozing was noted from the umbilical stump, with profound coagulopathy and anaemia being subsequently noted with initial haemoglobin (Hb) 3.5 g/dl, packed cell volume (PCV) 12%, prothrombin time (PT) >120 s and activated partial thromboplastin time (APTT) >360 s. He was transfused twice with 20 ml/kg of packed red blood cells (RBC) while on NICU (with an improvement in Hb to 10.3 g/dl) and given routine intramascular vitamin K. A cranial ultrasound (CUSS) on admission to NICU demonstrated multiple echobright areas in the parenchyma consistent with calcification, particularly in the region of the basal ganglia, and frontal cystic lesions, thought to be consistent with old/antenatal bleeding. Sepsis was suspected as a potential cause of coagulopathy, thus empirical intravenous antibiotics were started, with the addition of antiviral cover in view of the CUSS appearances.

The baby was transferred to the paediatric intensive care unit (PICU), aged 7 h, on a prostaglandin E2 (Prostin) infusion (10 ng/kg/min) in view of the antenatal diagnosis of aortic coarctation. Following desaturations on NICU since the start of the prostaglandin infusion, the baby was intubated and ventilated for transfer, sedated with morphine and neuromuscular blocked with vecuronium.

On arrival to PICU, the case history was reviewed: the baby's mother had previously undergone mechanical aortic and mitral valve replacements in Italy in 2010 for rheumatic valve disease, and had been warfarinised subsequently. It transpired that she had misinterpreted the advice from her cardiologist of: 'you cannot get pregnant whilst on warfarin', assuming that warfarin was in some way contraceptive, and therefore conceived while anticoagulated with warfarin. On discovering that she was pregnant, her anticoagulation was transitioned from warfarin to low molecular weight heparin (Enoxaparin) at 17/40 gestation. The mother unfortunately suffered a stroke (middle cerebral artery territory infarct) at 23/40 gestation and was therefore promptly restarted on warfarin, which was continued for the remainder of her pregnancy at a dose of 5–6 mg, with international normalised ratio (INR) 3–4.7.

In view of the above history (coagulopathy, evidence of bleeding, anaemia and maternal anticoagulation), on

arrival to PICU, the baby was suspected to be manifesting features of fetal warfarin syndrome. In the interim, the baby remained ventilated and haemodynamically stable; echocardiography demonstrated a structurally and functionally normal heart and excluded aortic coarctation, permitting discontinuation of the prostaglandin infusion. Empirical intravenous antibiotics and antivirals were continued to cover possible sepsis, though C reactive protein (CRP) was <1. Haematologically, anaemia was confirmed (Hb 10 g/dl following a total of 40 ml/kg of RBCs) with mild thrombocytopenia (Plts 104) and coagulopathy (PT 125, INR 10.3, APTT 178.1). The baby's blood group was confirmed to be O Rhesus positive and a negative Coombs/direct antiglobulin test (DAT) made haemolysis secondary to ABO/Rhesus incompatibility an unlikely aetiology of the anaemia. Liver function tests were within normal limits, suggesting an absence of impaired hepatic synthetic capacity as a cause of coagulopathy.

The dose of intramuscular vitamin K was repeated, fresh frozen plasma (10 ml/kg) was transfused, followed by a further 20 ml/kg of group-specific packed RBCs. Meanwhile, a Kleihauer-Betke test was requested from the transferring hospital, yielding a result of 5% fetal haemoglobin in the maternal circulation, suggestive of significant fetal–maternal haemorrhage.

Following the above treatment, the coagulopathy and anaemia quickly resolved. The baby subsequently remained stable, such that, in view of exclusion of congenital heart disease, transfer back to the local neonatal unit could occur 48 h after admission, where he was quickly extubated and antibiotics were discontinued with negative blood cultures and persistently non-elevated CRP. The baby was fit for discharge to the postnatal ward on day 7 of life, and then discharged home after progressing to full enteral feeding by day 13 (corrected gestational age of 36+5/40). All screening for a potential infective (viral and bacterial) aetiology yielded negative results.

Interestingly, although calcified regions noted on the CUSS prior to transfer to PICU were again observed on days 6 and 8 of life, the initial frontal cystic changes were no longer present. Subsequent neuroimaging in the form of brain MRI took place on day 40, demonstrating non-specific white matter changes along with mildly immature frontal folding and slightly increased frontal extra-cerebral space, but no cystic changes. When reviewed in the neurology outpatient clinic (day 49), it was felt that the results of the above are of uncertain clinical or prognostic significance, and that such white matter changes, in particular, are not uncommon in preterm babies and/or those with anaemia at birth. Clinically, the baby displayed no overt neurological deficit, with just a mild squint (normal for corrected gestational age).

DIFFERENTIAL DIAGNOSIS

- Fetal warfarin syndrome
- Neonatal sepsis
- *In utero* TORCH infection
- Primary disorder of coagulation

TREATMENT

- Vitamin K
- Fresh frozen plasma
- Blood transfusion (packed RBC)
- Fluid resuscitation
- Empirical IV antibiotics
- Empirical IV antivirals
- Initial prostaglandin E2 infusion

OUTCOME AND FOLLOW-UP

At hospital discharge, the baby was clinically well with a normal coagulation profile and full blood count. The antenatal diagnosis of congenital heart disease was excluded postnatally.

Subsequent MRI brain demonstrated findings that may be in keeping with the baby's gestational age, and are of equivocal significance. There is no clinically demonstrable neurological deficit.

DISCUSSION

The use of vitamin K antagonists such as warfarin during pregnancy carries the potential for fetal malformation, especially if administered during the first trimester. Between 6 and 12 weeks of gestation, fetal synthesis of proteins integral to bone and cartilage formation may be impaired by transplacental passage of warfarin, resulting in the well-defined warfarin embryopathy.[1] Furthermore, the teratogenicity of warfarin is seemingly dose-dependent, with more frequent and more serious malformations occurring when warfarin doses of >5 mg/day are required to maintain a therapeutic prothrombin time.[2]

Warfarin embryopathy, also known as fetal warfarin syndrome or di Sala syndrome, is primarily characterised by nasal hypoplasia and skeletal abnormalities, including short limbs and digits (brachydactyly), and stippled epiphyses.[3 4] A systematic review of data pertaining to pregnancies anticoagulated for maternal prosthetic heart valves reported that, of 41 live births born with malformations following maternal warfarinisation, 29 had classical nasal hypoplasia and epiphysial stippling, while 4 had neurological anomalies (hydrocephalus and learning difficulties), 4 had cleft lip and/or palate and a further 4 had isolated anomalies of one organ system.[5] While there are numerous reported cases of warfarin embryopathy, fetal haemorrhage associated with maternal warfarinisation is a relatively rare phenomenon, the incidence of which may not be predictable from maternal INR.[6–8] The case we report is phenotypically novel in that it was characterised by isolated fetal coagulopathy and haemorrhage, likely reflecting continued warfarinisation up to parturition.

An optimal anticoagulation regimen for pregnant women with mechanical heart valves would be both efficacious in preventing maternal thromboembolic events while non-deleterious to the developing fetus; however, consensus regarding such a regimen remains elusive: warfarin is associated with well-documented embryopathy and significant rates of fetal attrition, while suboptimal anticoagulation renders an individual already at increased risk of thromboembolic events, more susceptible than usual during the hypercoagulable state of pregnancy. Much of the available published literature reports on the relative safety (to mother and fetus) and efficacy of anticoagulation regimens in pregnancy that include oral anticoagulants (almost exclusively warfarin or derivatives thereof) alone, low-dose or adjusted-dose subcutaneous heparin (low molecular weight or unfractionated heparin),

BMJ Case Reports 2012; doi:10.1136/bcr-2012-007344

or a combination of the two, often with warfarin being converted to heparin during the vital first trimester (and almost universally, peripartum).

The above is illustrated by a systematic review of the literature published in 2000, pooling data from 28 published studies (8 prospective studies), comprising a total of 976 women during 1234 pregnancies.[5] As well as comparing the above three regimens, a further 'control' group was reported who received no anticoagulants (antiplatelet medications were not considered as anticoagulants) during pregnancy. Overall rates of fetal wastage (spontaneous abortion, stillbirth and neonatal death) were 19.6% in the control group (no difference between those receiving antiplatelet agents and no medication at all), compared to 33.6% when warfarin was used alone (the case in 69% of pregnancies reported) and 42.9% with heparin used in isolation throughout pregnancy. Substitution of warfarin for heparin at or prior to 6-week gestation reduced rates of fetal wastage to 16.3%, a benefit that was not observed when heparin replaced warfarin after a 6-week threshold (35.7% fetal loss). Use of heparin alone or early first-trimester conversion (≤6 weeks) from warfarin to heparin entirely prevented the incidence of congenital anomalies. Without conversion (warfarin throughout), malformations occurred in 6.4%, and with conversion after 6 weeks, 11.1% had demonstrable embryopathy.

Although early conversion from warfarin to heparin seems compellingly advantageous to the fetus (significantly less fetal wastage and apparent abolition of embryopathy), this benefit is outweighed by the increased risk conferred upon the mother. More than twice as many maternal thromboembolic events (TEE) occurred following first-trimester conversion from warfarin to heparin (3.9% vs 9.2%), and use of heparin alone resulted in TEE in as many as a third of pregnancies (though this group was numerically very small). Similarly, maternal death rates were doubled when warfarin was switched to heparin in the first trimester (1.9% and 4.2%, respectively), and dramatically elevated (15.6%) with the use of heparin alone.

A review of the literature published over the subsequent 10 years (4 studies being prospective), comprising 1343 pregnancies (62% of which were anticoagulated with warfarin alone throughout), chronicles a remarkably similar story.[8] Fetal wastage rates with warfarin alone were 32.9%, decreasing to 19.9% with early conversion to heparin (38.8% with heparin alone). Early first-trimester conversion to heparin or use of heparin throughout again precluded warfarin-related embryopathy, albeit at the expense of significantly more frequent maternal complications: warfarin throughout pregnancy was associated with a 2.9% risk of maternal TEE and a 1.1% incidence of maternal death; these risks were approximately doubled following early conversion to heparin (7.1% and 1.7%, respectively), and quadrupled with sole use of heparin throughout pregnancy (13.4% and 4.7%, respectively).

Overall, two systematic literature reviews, one covering the era prior to the year 2000 and the latter, the first 10 years of the new millennium, report almost identical findings despite supposed advances in prosthetic valve material towards less thrombogenic materials. While some authors report that the incidence of fetal warfarin syndrome has been hitherto overestimated, they are in the overwhelming minority.[9] Warfarin provides the greatest thromboprophylactic benefit to mothers but is associated with appreciable rates of fetal wastage and congenital malformations. Conversion of warfarin to heparin in the pivotal period prior to 6-week gestation reduces rates of fetal attrition and prevents congenital anomalies attributable to warfarin; however, this is at the expense of significantly increasing the maternal risk of thromboembolic complications and death, a risk which is further elevated when heparin is used alone throughout pregnancy (without the benefit of reduced fetal wastage).

The limitations of data published thus far include a paucity of prospective studies and incomplete information, particularly pertaining to modes of heparinisation and monitoring thereof. More recent studies have reported questionable benefit in terms of adverse maternal outcomes from the use of adjusted-dose low molecular weight heparin, with seemingly therapeutic anticoagulation not necessarily conferring protection from TEE in pregnancy.[10 11] There is a clear need for further well-designed prospective studies in this area.

The above emphasises the challenging clinical conundrum of anticoagulation in pregnancy and reiterates that, even with close monitoring and good compliance, incidence of adverse outcomes for mother and fetus remains high. This population of expectant mothers is a complex and heterogeneous one with multiple variables, not least prosthetic valve position and type, cardiac function, and presence of arrhythmia, thus an optimised anticoagulation regimen in pregnancy is likely to be one tailored to the individual. Common to all cases is the requirement for excellent provision of information and clear communication between healthcare professionals and parents, ensuring that decisions made regarding pregnancy in the context of maternal anticoagulation, can be fully informed ones.

Learning points

- When faced with an unexpected neonatal presentation, careful consideration of the maternal medical and drug history is mandatory.
- Fetal warfarin syndrome is a relatively uncommon phenomenon of varying phenotype, including dysmorphism, skeletal anomalies and fetal coagulopathy.
- Anticoagulation in pregnancy is challenging: there is little consensus regarding an optimum regimen, which is both non-teratogenic and effective in preventing maternal adverse events.
- In view of the appreciable risks (to mother and fetus) of anticoagulation in pregnancy, patients must be well informed, permitting educated decision-making.
- This case is relevant to a number of clinicians: adult cardiologists, paediatric and fetal cardiologists, neonatologists, paediatric neurologists, paediatric intensivists, haematologists and obstetricians.

Competing interests None.

Patient consent Obtained.

Correction notice This article has been corrected since it was published online on the 1 November 2012. The corresponding author's e-mail address has been corrected.

REFERENCES

1. **Walfisch A,** Koren G. The 'warfarin window' in pregnancy: the importance of half-life. *JOGC* 2010;**32**:988–9.
2. **Vitale N,** De Feo M, De Santo LS, *et al*. Dose-dependent fetal complications of warfarin in pregnant women with mechanical heart valves. *J Am Coll Cardiol* 1999;**33**:1637–41.
3. **Sathienkijkanchai A,** Wasant P. Fetal Warfarin syndrome. *J Med Assoc Thai* 2005;**88**(Suppl 8):S246–50.
4. **Kumar M,** Bhasker SK, Singh R, *et al*. Di Sala syndrome. *BMJ Case Rep* 2012;10.1136/bcr.12.2011.5291, Published 20 March 2012.
5. **Chan WS,** Anand S, Ginsberg JS. Anticoagulation of pregnant women with mechanical heart valves: a systematic review of the literature. *Arch Intern Med* 2000;**160**:191–6.
6. **Lee HC,** Cho SY, Lee HJ, *et al*. Warfarin-associated fetal intracranial hemorrhage: a case report. *J Korean Med Sci* 2003;**18**:764–7.
7. **Masamoto H,** Uehara H, Mekaru K, *et al*. Warfarin-associated fetal intracranial hemorrhage in woman with mitral valve replacements: a case report. *Am J Perinatol* 2009;**26**:597–600.
8. **Oswal K,** Agarwal A. Warfarin-induced fetal intracranial subdural hematoma. *J Clin Ultrasound* 2008;**36**:451–3.
9. **Geelani MA,** Singh S, Verma A, *et al*. Anticoagulation in patients with mechanical valves during pregnancy. *Asian Cardiovasc Thorac Ann* 2005;**13**:30–3.
10. **Basude S,** Hein C, Curtis S, *et al*. Low-molecular-weight heparin or warfarin for anticoagulation in pregnant women with mechanical heart valves: what are the risks? A retrospective observational study. *BJOG* 2012;**119**:1008–13.
11. **Yinon Y,** Siu SC, Warshafsky C, *et al*. Use of low molecular weight heparin in pregnant women with mechanical heart valves. *Am J Cardiol* 2009;**9**:1259–63.