CASE REPORT

Low-dose warfarin maternal anticoagulation and fetal warfarin syndrome

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SUMMARY

Fetuses exposed to warfarin during pregnancy are at an increased risk of developing an embryopathy known as fetal warfarin syndrome or warfarin embryopathy. The most consistent anomalies are nasal hypoplasia and stippling of vertebrae or bony epiphyses. Management of pregnant patients on anticoagulation is challenging. Current guidelines suggest the use of warfarin if the therapeutic dose is ≤ 5 mg/day. We report the case of a newborn with signs of warfarin embryopathy born from a mother anticoagulated with warfarin due to mechanical mitral and aortic heart valves. Warfarin was required at the dose of 5 mg/day and was withheld without medical advice between weeks 8 and 10 with no other anticoagulation. The newborn presented with skeletal abnormalities and a ventricular septal defect that have not required specific treatment during the first year of life. Low-dose warfarin is associated with a lower risk of warfarin-related fetopathy but the risk of embryopathy seems unchanged.

BACKGROUND

Warfarin is a coumarin anticoagulant that has been in clinical use for over 50 years. It acts by depressing the synthesis of vitamin K-dependent clotting factors (factors II, VII, IX and X) by inhibiting vitamin K epoxide reductase. Warfarin crosses the placenta and its use during pregnancy may cause stillbirth, spontaneous abortion, neonatal death, premature delivery and a variety of congenital anomalies known as fetal warfarin syndrome (FWS), warfarin embryopathy or Di Sala syndrome.^{1,2} Sequelae following intrauterine warfarin exposure may occur from exposure during either the embryonic or the fetal period and the time of greatest susceptibility is from the 6th to the 12th week of gestation.^{3,4} The teratogenic effect appears to be dose dependent with more frequent and serious malformations occurring with doses above 5 mg/day.⁵ FWS has been identified in 15%–25% of fetuses exposed to warfarin during the first trimester.^{1,2} The most consistent fetal anomalies are nasal hypoplasia and stippling of vertebrae or bony epiphyses. Newborns exposed to warfarin during the three trimesters of gestation are at highest risk for development of serious effects such as blindness, deafness and development delay.

Pregnancy in women with mechanical heart valves is associated with significant maternal and fetal risks. To prevent serious thromboembolic

complications, therapeutic anticoagulation is required in all pregnant women with mechanical heart valves. None of the currently available anticoagulation options are without risk for the mother or the child, and when the outcomes of both mother and fetus are considered, no regimen is clearly superior.⁶ Anticoagulation options include vitamin K antagonists (such as warfarin), heparins—low-molecular-weight heparin (LMWH) and unfractionated heparin (UFH) and sequential treatment with heparin (most commonly LMWH) during the first trimester and vitamin K antagonists during the second and third trimester. Although warfarin's use during pregnancy can cause FWS, it is the safest anticoagulant for the mother, associated with the lowest rates of maternal thromboembolic complications and maternal mortality.^{7,8} A recently published meta-analysis on maternal anticoagulation and maternal and fetal outcomes reported that the use of vitamin K antagonists with standard (2.5–3.5) international normalised ratio (INR) targets throughout pregnancy was associated with the lowest proportion of maternal mortality (0.9%, 95% CI 0.1% to 1.6%) and thromboembolic complications (2.7%, 95% CI 1.4% to 4.0%) followed by sequential treatment (2%, 95% CI 0.8% to 3.1% and 5.8%, 95% CI 3.8% to 7.7%) and LMWH (2.9%, 95% CI 0.2% to 5.7% and 8.7%, 95% CI 3.9% to 13.4%).⁹ LMWH throughout pregnancy was associated with the highest number of live births followed by sequential treatment and vitamin K antagonists throughout pregnancy. According to the European Society of Cardiology (ESC) and the American Heart Association/American College of Cardiology (AHA/ACC) guidelines,^{10,11} continuation of warfarin throughout pregnancy should be considered when the therapeutic dose is ≤ 5 mg daily because of the low risk of fetopathy ($<3\%$) and safety profile for the mother. The ESC guideline states that discontinuation of warfarin and a switch to UFH or LMWH between weeks 6 and 12 under strict dose control and supervision may also be considered for these patients. When the therapeutic dose of warfarin is >5 mg/day, the ESC guideline suggests discontinuation of warfarin between weeks 6 and 12 and replacement by adjusted-dose UFH (activated partial thromboplastin time (aPTT) ≥ 2 times the control) or LMWH two times a day with dose adjustment according to weight and according to anti-Xa levels, and the AHA/ACC guideline suggests switching to LMWH administered at least two times a day during the first trimester with close monitoring.

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Figure 1 Lateral view of the face of the newborn with evidence of nasal hypoplasia.

In pregnant women with mechanical heart valves it is very important to discuss with parents the available options for maternal anticoagulation and the maternal and fetal risks associated with each regimen.

CASE PRESENTATION

A male newborn was delivered with sequelae characteristics of FWS. He was born via caesarean section at 39 weeks of gestation to a 25-year-old woman, gravida 1 para 1, chronically anticoagulated with warfarin since age 11 because of mechanical mitral and aortic valve replacement following rheumatic heart disease. Warfarin was maintained at the dose of 5 mg/day with

Figure 2 Stippling of lumbosacral vertebrae and epiphyses of the femurs.

Figure 3 Lower limbs radiography showing bilateral stippling of calcaneus and tarsal bones.

INR between 2.5 and 3.5 until week 8 of gestation. Anticoagulation was suspended at week 8 (without medical advice) and was resumed at week 10 with warfarin and LMWH. LMWH was suspended at week 12 (with therapeutic INR) and warfarin maintained at 5 mg/day until week 39 of gestation.

A fetal echography performed at 21 weeks of gestation showed absence of nasal bones, small nostrils and malformation of the lumbosacral vertebrae with apparent opening of the last vertebral bodies. The same dysmorphias were found at the echography performed at 30 weeks. A fetal echocardiography performed at 28 weeks showed a small muscular ventricular septal defect.

At 39 weeks the mother was admitted for elective caesarean. Warfarin was suspended and switched to UFH. The newborn was delivered with an Apgar score of 7/9/10 with no need for resuscitation. Birth weight was 3.65 kg (50th percentile), length 49 cm (10th percentile) and head circumference 35 cm (25–50th percentile). The newborn presented with nasal hypoplasia, depression of the nasal pyramid, small nose on facial profile view and noisy breathing sounds (see [figure 1](#)). The nasal fossae were only permeable to a 5-frame calibre catheter. He was transferred to the neonatal intensive care unit and developed respiratory distress with need for non-invasive ventilation (with high-flow oxygen and continuous positive airway pressure) during the first 36 hours of life. During the first two weeks of life, the newborn maintained noisy breathing sounds with tachypnoea and intercostal retraction with distress, feeding difficulties with fatigue and moderate axial hypotonia. He was discharged home at one month of age with no specific treatment and with follow-up at ophthalmology, audiology, paediatric neurology, neonatology, child development and paediatric cardiology clinics. At one year of age the infant is asymptomatic and has had a normal development.

INVESTIGATIONS

To further investigate the nasal hypoplasia and noisy breathing sounds, a nasal fibroscopy was performed. It showed stenosis of the medium region of the left nasal fossae and a smaller right nasal fossae with three regions of stenosis: anterior, medial and posterior. The X-ray scans showed stippling of lumbosacral vertebrae, epiphysis of the femurs, calcaneus and tarsal bones (see [figures 2 and 3](#)). The transfontanellar ultrasound performed to study cerebral malformations associated with this syndrome was normal. Transthoracic echocardiography showed a small restrictive muscular ventricular septal defect. At one month, ophthalmological examination was normal. Audiometric findings revealed auditory evoked potentials absent bilaterally at birth but normal at 6 months.

DIFFERENTIAL DIAGNOSIS

In this case as the findings were consistent with sequelae associated with maternal intake of warfarin during pregnancy, no further aetiological studies were performed. Chondrodysplasia punctata is a group of rare genetic diseases that also presents with stippled epiphyses and skeletal changes.

TREATMENT

Treatment depends on the congenital anomalies present and their implications for the well-being of the infant. In this case during the first year of life no specific treatment was required. The newborn required supportive treatment with non-invasive ventilation during the first 36 hours of life for hypoplasia and stenosis of the nasal fossae.

OUTCOME AND FOLLOW-UP

The prognosis of FWS depends on the severity of the in utero acquired defects. After discharge, the newborn was referred to ophthalmology, audiology, paediatric neurology, neonatology, child development and paediatric cardiology clinics.

The infant was referred to ophthalmology examination because of the possible ophthalmological involvement in FWS. Observations and examinations were normal and he was discharged from ophthalmology clinics. Audiometric findings revealed auditory evoked potentials absent bilaterally at birth but normal at 6 months, and the infant was discharged. The newborn was initially referred for neurology evaluation because of axial hypotonia that resolved gradually over the first few months of life. Since hypotonia resolved and the infant has had a normal development, he was discharged from neurology and child development clinics. The infant is followed up by paediatric cardiology because of a small restrictive ventricular septal defect. At 1 year of age, the infant maintains follow-up at general paediatrics and paediatric cardiology clinics.

DISCUSSION

After the first reports linking warfarin intake and congenital malformations in newborns in 1960s, in 1975 there was the recognition of this association in five infants.^{5,9} The most consistent fetal anomalies described are nasal hypoplasia, depressed nasal bridge, stippling of uncalcified epiphyses (most frequently affecting the axial skeleton, proximal femur and calcaneus), mild hypoplasia of the nails and shortened fingers. Franco *et al*¹² suggested that warfarin may inhibit arylsulfatase enzyme activity, the cause of X-linked recessive chondrodysplasia punctata which is phenotypically similar to warfarin embryopathy.⁴ Although warfarin seems to be the safest anticoagulation for pregnant women with mechanical heart valves, this treatment is associated with the risk of congenital malformations in the newborn.

As pointed out by some authors,^{13,14} although low doses of warfarin during the first trimester are associated with a lower rate of warfarin-related fetopathy than higher doses of warfarin, the risk of warfarin-related embryopathy is still present. Some studies have shown that with lower doses of warfarin the risk of FWS is lower,⁹ but other studies have shown that this risk is unchanged.^{15–17} There are some examples in the literature of cases as the one we report with newborns presenting with features of FWS despite low doses of warfarin.^{18–20}

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 newborn presented with skeletal abnormalities typical of FWS and a ventricular septal defect. Despite these

congenital malformations, the infant has required no specific treatment during the first year of life and has had a normal development.

In pregnant women with mechanical heart valves, it is very important to discuss with parents the available options for anticoagulation during pregnancy, with careful discussion of the maternal and fetal risks of each regimen.

Learning points

- ▶ Management of anticoagulation during pregnancy is challenging. Available options must be discussed with parents.
- ▶ Although warfarin is the safest anticoagulation option for pregnant women, its use during pregnancy is associated with the risk of fetal warfarin syndrome (FWS).
- ▶ Low-dose warfarin during pregnancy reduces the risk of stillbirth but the risk of FWS is mildly reduced or unchanged.
- ▶ Newborns with possible FWS should be investigated after birth so that in utero defects can be investigated and eventually corrected in a timely manner in order to reduce their possible effects on the child's growth and development.

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