Intrauterine Death of Twin II Associated With Hereditary Thrombophilia

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By OBGYN.net Staff [1]

A Case of Prenatal Renal Vein Thrombosis, Intrauterine Death of Twin II Associated With Hereditary Thrombophilia

A 33 years old Caucasian woman with a previous healthy male child was booked into the antenatal Clinic at 11 weeks gestation. Ultrasound scan confirmed a viable dichorionic twin pregnancy. Antenatal progress was uncomplicated and serial ultrasound scans demonstrated normal growth, normal liquor volume and normal Doppler flow of both twins until 32 weeks.

At 34 weeks gestation she went into premature labour and both twins were delivered vaginally. The first twin (male) was cephalic presentation and born with Apgar scores of 5 and 8 at 1 minute and 5 minutes respectively and weighed 2.54 kg. The second twin (female), also cephalic presentation diagnosed as an intrauterine death (IUD) and a macerated stillborn weighing 1.94 kg was delivered. Two separate placentae confirmed dichorionicity, but were not sent for histopathology. The autopsy on the stillbirth confirmed an anatomically normal female baby. There was significant maceration in keeping with IUD more than 7 days before delivery but failed to reveal any congenital malformations. The only abnormality found at autopsy was extensive renal vein thrombosis (RVT) with calcification which suggested possible primary thrombotic disorder in the fetus such as protein C deficiency.

On further inquiry into the family history, the father of the baby was found to have congenital protein C deficiency. This was first diagnosed when he had a thrombotic episode after surgery for Crohn’s disease at the age of 20. He is currently on Warfarin therapy and is under the care of the Haematologist. A similar problem was also recorded in his mother (grandmother of the baby). The possible link between the symptomatic heritable thrombophilic defect in the family and the extensive renal vein thrombosis resulting in IUD of twin II was appreciated and the family was referred to the Haematologist for further screening for congenital thrombophilia. It was later discovered that the mother of the children has also inherited congenital protein S deficiency. The maternal family history was not available as she had been adopted as a child. Among the two boys, one is positive for congenital protein C deficiency and the other one is positive for protein S deficiency. It is possible that the twin II might have inherited both protein C and S deficiency resulting in extensive venous thrombosis leading to IUD.

Discussion
This is thought to be the first case reported in the literature where the entire family is affected with congenital thrombophilia transmitted to the offsprings. This case also illustrates the need to think of inherited thrombophilia as a primary cause of prenatal extensive RVT. Inherited thrombophilia is known to be associated with an increased risk of thrombosis. The heritable defects which are at present accepted as proven to be associated with familial venous thrombosis are deficiency of antithrombin (AT), protein C (PC) or protein S (PS), Activated Protein C Resistance (APCR) and Factor V (FV) Leiden mutation. Women with a family history of these defects are at an increased risk of pregnancy-associated venous thrombosis and increased risk of fetal loss and other vascular complications of pregnancy.

Renal vein thrombosis (RVT) occurs at any time in the neonatal period and also has been described in-utero. Prenatal RVT is a less common entity found incidentally on prenatal imaging or at autopsy. Calcification due to RVT has been reported as early as the first day of life, indicating a prenatal origin.

In neonates, RVT occurs as an acute and life-threatening event as a result of perinatal stress, most frequently dehydration. Predisposing factors for neonatal RVT include asphyxia, shock, traumatic delivery, dehydration, polycythemia, sepsis, congenital heart disease, congenital renal vein defects and rarely primary renal disease. It is more common in babies of diabetic mothers or when maternal
dehydratation or toxaemia has occurred. There is also a recognised association with congenital defect of antithrombin proteins. Bilateral RVT and venous sinus thrombosis in a neonate associated with Factor V mutation has been reported.

In this case presented there was no history of diabetes and the antenatal period was uncomplicated with both twins growing normally until 32 weeks. The mother was not aware of any reduction in fetal movement until she went into premature labour at 34 weeks. The labour progressed quite fast with no evidence of fetal distress. However the autopsy findings suggested the intrauterine death had occurred at least 7 days before delivery. Although the cause of death due to placental disease was not excluded as the placenta were not sent for histopathology, the autopsy did not reveal any congenital abnormalities except extensive RVT with calcification. Further follow-up investigations at the haematology clinic revealed the whole family have been affected with congenital thrombophilia. It is possible that the twin two might have inherited both protein C and S deficiency resulting in extensive venous thrombosis leading to IUD.

Heritable deficiencies of components of the antithrombin and protein C and protein S systems are more common than was originally realised. Screening studies have demonstrated reduced antithrombin function in 1 in 200 - 400 individuals and protein C deficiency in 1 in 300 -500. No large study has so far reported on the prevalence of protein S deficiency in healthy subjects. The FV Leiden mutation is extremely prevalent (2 - 7 %) in populations of European extraction, but much less common or even absent in other populations.

It has been shown that there is an increased risk of fetal loss in women with deficiencies of antithrombin, protein C or protein S – the risk appearing to be greatest for women with antithrombin deficiency and in women who have been shown to have more than one thrombophilic gene defect. Although the increased risk of fetal loss is present throughout the pregnancy, the effect of thrombophilia is particularly marked with respect to fetal loss occurring after 28 weeks’ gestation. Inevitably, with the developing interest in the potential role of genetic thrombophilic defects in VTE and other complications of pregnancy has come pressure to screen women for these abnormalities. Previously it was suggested that all women from symptomatic kindred with protein C – S system defects (whether or not they had already had a previous thrombotic event) should be offered anticoagulant prophylaxis during pregnancy, at least during the third trimester. However, with the increasing evidence that, at least in the case of protein S deficiency and FV Leiden, the risk may be mainly post-partum, it may be acceptable to delay anticoagulant prophylaxis in asymptomatic women with protein S deficiency or FV Leiden until closer to delivery or even to restrict it to the post-partum period only.

It remains important to assess thrombotic risk in each individual patient, to re-assess changing risk as pregnancy progresses and to maintain a flexible policy on the timing of introduction of anticoagulant prophylaxis – particularly in asymptomatic women with abnormalities in their protein C – protein S system.

It was reported that the incidence of thrombosis occurring during pregnancy in protein C and protein S deficient women, respectively is 7% and 0%, and is significantly less than the incidence of post-partum thrombotic events – 19% in protein C deficiency and 17% in protein S deficiency. This has been further confirmed by other workers. This explained why this woman has not had any thrombotic event during her two pregnancies. Both clinically recessive and dominant forms of congenital PC deficiency are recognised - the clinically recessive type being more common. Congenital PS deficiency is inherited as an autosomal dominant trait.

Homzygous PC deficient infants are either stillborn or suffer perinatal purpura fulminans with widespread thrombosis of blood vessels. These patients have undetectable levels of PC and the parents have values consistent with heterozygous state. A similar condition has occurred in an infant with homzygous PS deficiency. In heterozygous deficiency there is no detectable association with a risk of thrombosis until additional risk factors, such as surgery, are encountered. Parents should be aware that all the heritable thrombophilic defects are transmitted autosomally and that statistically, each of their children has a 50/50 chance of being affected. It is unusual to suffer venous thrombosis in healthy children unless some acquired thrombotic trigger supervenes.

Currently it seems reasonable to focus resources on pregnant women from symptomatic families rather than screening whole populations for these defects. Careful and repeated counseling is necessary and individuals with heritable thrombophilic defects should be regularly reviewed at specialist clinics and ready access to immediate expert advice. Prenatal duplex doppler ultrasonographic detection of RVT both in fetus and newborn is recommended in the affected family.
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