LETTERS to the EDITOR

Fetal intraventricular haemorrhage and maternal warfarin

SIR,—Prenatal ultrasonography has documented the association between fetal intracranial haemorrhage and maternal epileptic seizures, severe hypertensive or hypotensive episodes, viral infection, and alloimmune thrombocytopenia.[1] Postnatal studies have also implicated maternal anticoagulant therapy as a cause of intracranial haemorrhage, which was thought to occur during delivery.[2] We report prenatal diagnosis of fetal intraventricular haemorrhage as a result of maternal anticoagulation with warfarin.

In the first case, the mother had pulmonary embolism at 26 weeks' gestation. She was given intravenous heparin 30 000 U per day and then warfarin 6 mg per day. Initially anticoagulation was satisfactory (prothrombin internal normalised ratio [INR] 2·5), but on the 10th day, INR rose to 8·6. The mother was given intravenous vitamin K 0·5 mg and the dose of warfarin was reduced to 3 mg daily. INR stabilised at 1·7–2·5. At 33 weeks' gestation, fetal ultrasound demonstrated an undulating hyperechogenic intracranial mass with contralateral ventriculomegaly (figure) and a large posterior fossa cyst with cerebellar hypoplasia. Fetal blood taken by cordocentesis revealed severe anaemia (haemoglobin 6·2 g/dL, normal mean 13·4) and reticulocytosis ($0·55 \times 10^{12}$/L, normal mean $0·17 \times 10^{12}$); blood gases and platelet and leucocyte counts were normal. Fetal procoagulant factors II, VII, IX, and X (0, 7, 2 and 3·5 IU/dL, respectively) were profoundly depressed (normal 14–24 for factors II, VII, and X, and 6–12 for IX). In maternal blood, only factors II and X were below normal. Warfarin concentrations in fetal and maternal blood were similar (0·3 and 0·5 μg/mL); the therapeutic range in adult patients during stable antiocoagulation is 0·7–3·2 μg/mL (mean 1·6, n = 56). The fetus died at 36 weeks' gestation and necropsy confirmed a massive intracranial haemorrhage with cerebral atrophy.

In a second case, the mother was on long-term warfarin for aortic and mitral valve disease. During the first 15 weeks of pregnancy, anticoagulation was changed to subcutaneous heparin 14 000 U per day). She was then treated with warfarin 5–6 mg daily and INR was 0·7–1·9. Serial ultrasound demonstrated normal fetal growth and anatomy but at 29 weeks the fetus died. There was prenatal ultrasonographic and necropsy evidence of massive intraventricular haemorrhage.

Fetal intraventricular haemorrhage.

Undulating hyperechogenic intracranial mass with contralateral ventriculomegaly.

These cases illustrate the hazards of anticoagulation with warfarin during pregnancy. Although in the first case fetal intracranial haemorrhage could be attributed to the sudden surge in maternal INR to 8·6, INR was always normal in the second. The fetus is susceptible to risk of haemorrhage because of several interrelated factors focused on fetal vitamin K metabolism. In normal mid-gestation fetuses, hepatic stores of vitamin K_2 are undetectable and vitamin K_1 is only 20% of that in adults;[3] this is reflected in the physiologically low concentrations in fetal blood of the vitamin-K-dependent procoagulant factors. Even in subtherapeutic doses, warfarin reduces fetal vitamin K further to the point where normal haemostasis is jeopardised. When over-anticoagulation occurs, administration of standard doses of vitamin K to the mother is unlikely to reverse the effects on the fetus since the maternofetal concentration gradient for vitamin K is 20–40 to 1.[3] In addition, maternal coagulation indices did not predict safety in the fetus. Where a risk to the fetus is suspected, it may be necessary to do cordocentesis to assess fetal coagulation and, if indicated, consider intrauterine transfusion of fresh frozen plasma and vitamin K to reverse the effects of warfarin.

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Oral clonidine for heart rate control in chronic atrial fibrillation

SIR,—In chronic atrial fibrillation digoxin is the most suitable drug to control ventricular rate.[1] However, the addition of a beta or calcium-channel blocker is often required.[2] Unfortunately some patients are non-responders even to these combinations, and others have adverse effects.[3] Roden et al[4] evaluated the electrophysiological and haemodynamic effects of chronic oral clonidine 0·2–0·5 mg every 12 h in hypertensive patients. At doses that modestly lowered diastolic blood pressure, clonidine significantly reduced sinus rate and increased atrial pacing, producing the atrioventricular nodal Wenckenbach phenomenon. Clonidine also significantly increased corrected sinus node recovery time. Roth et al[5] used a single low dose (0·075 mg) of clonidine to control ventricular response in emergency cases with rapid atrial fibrillation.

To assess the efficacy of clonidine in ambulatory patients with chronic atrial fibrillation with fast ventricular response (resting heart rate >90/min) who were not well controlled by digoxin (0·250–0·375 mg daily), we studied 17 consecutive patients (6 males; mean age 70 [SD 10] years). All patients were maintained on digoxin throughout study. They had haemodynamically stable,