Constriction of the fetal ductus arteriosus may occur during treatment of premature labor with indomethacin. This article includes a report of such a case, as well as a discussion of the Doppler methods of evaluation of the fetal ductus arteriosus and the current understanding of the clinical implications of abnormal findings.

CASE REPORT

I. S. was a para 0, Ab 2 woman at 28 weeks' gestation. Two weeks before admission, premature uterine contractions began and increased in frequency. Oral terbutaline was used effectively to stop the contractions but caused tachycardia and failed to stop labor before admission. Amniocentesis was attempted to rule out infection as a cause of premature labor but was unsuccessful because of an anterior placenta. Ultrasound showed the baby to be active. There was no evidence of occult abruption. Contractions continued at every 10 minutes in spite of intravenous ritodrine up to 250 µg per minute. Doppler examination of the heart revealed increased systolic velocity at the ductus arteriosus (Figure 1). Because there was no elevation of diastolic velocity, this finding was not compatible with ductal constriction but only with the increased velocity in systole associated with the increased cardiac output effects of ritodrine. The woman was given 25 mg indomethacin orally every 6 hours and had immediate cessation of contractions. She was examined again by Doppler 24 hours after starting therapy. At that time there was a marked elevation of both systolic and diastolic velocities (Figure 2), typical of ductal constriction. Another finding that was not present on the previous examination was tricuspid regurgitation. At this point indomethacin was continued and the ritodrine infusion was weaned. Dexamethasone was given for fetal pulmonary maturation. The following day there were no further contractions; Doppler showed increased tricuspid regurgitation and there was mild right atrial enlargement. The indomethacin was stopped and terbutaline was continued, without recurrence of preterm labor. Serial Doppler studies during the next few days documented a return to baseline values for the ductal velocity. The tricuspid regurgitation continued for only 48 hours after signs of ductal constriction had resolved. Chronic administration of terbutaline was used in small doses to maintain tocolysis. The fetus was maintained in utero until 37 weeks' gestation and had an uncomplicated postnatal course.

METHODS

The normal ductal velocity increases with gestational age, and the maximal systolic and diastolic velocities are 140 and 35 cm per second (Figure 3). The fetal ductal arch is evaluated from sagittal scans. The maximal velocity is obtained by multiple attempts until the typical waveform is obtained. Image-directed continuous wave Doppler is ideally suited for detection of the maximal velocity in the ductus because it can measure very high velocities and because the max-
Figure 1  Echocardiographic imaging-directed continuous wave Doppler showing the increased systolic velocities consistent with increased flow in the ductus and not typical of constriction of the ductus. m/s, Meters per second.

Figure 2  Elevated systolic (2.5 meters per second) and diastolic (0.5 meters per second) velocities in the fetal ductus typical of constriction (upper panel). Tricuspid valvular regurgitation (lower panel) with a peak velocity of 3 meters per second occurred during constriction. TV, Tricuspid valve.

inal velocity, not its location, is the most important factor. The diagnosis of ductal constriction by Doppler is made by an increase in both the systolic and the diastolic velocities. Before administration of indomethacin, there was an increase in only the systolic velocity, which did not meet these criteria. The diagnosis of constriction after 24 hours of indomethacin administration in this case was based on the maximized ductal velocities of greater than 200 cm per second systolic and 100 cm per second diastolic, which were measured by continuous wave Doppler. By use of the Bernoulli assumption (that the velocity can be converted to pressure gradient in millimeters of mercury [mm Hg] by four times the velocity squared), this Doppler finding translates to a pulmonary artery to descending aorta gradient of 6 to 16 mm Hg. The fetus tolerated this increased afterload for 24 hours but, because of the onset of enlargement of the right side of the heart and qualitatively more tricuspid valve regurgitation at 48 hours, the medication was stopped. In practice, intermittent use of indomethacin (as in this case) is effective and has caused no long-term sequelae.

DISCUSSION

Constriction of the ductus arteriosus is a normal event after birth, but may occur in the human fetus when drugs that inhibit prostaglandin synthetase are taken by the mother. The mechanism by which this effect is suspected to compromise the fetus is thought to be right ventricular dysfunction. Constriction of the ductus may occur naturally and can lead to the
finding of decreased right ventricular shortening and tricuspid valvular regurgitation (Figure 1). Over the last decade, information about this effect has been accumulated in animal models, including fetal lambs, mice, and piglets. These studies have documented that not only are there changes in the ductus with a variety of prostaglandin inhibitors, but long-term exposure may lead to changes in the pulmonary arteries and the right ventricle. The latter changes are thought to be caused by chronic constriction or closure that causes elevated pressure in the main pulmonary artery and increased pulmonary arterial flow as a consequence. Successively more severe constriction of the fetal lamb ductus arteriosus has been shown to be reflected in increasing diastolic pulmonary to aortic pressure gradient (Figure 4). Therefore the severity of constriction appears to be related to the elevation in the diastolic velocity.

This may be thought of as acquired pulmonary vascular disease, which elevates the pulmonary vascular resistance. Direct effects of prostaglandin inhibition may also play a role. The pathologic findings are similar to those found when ducital ligation is performed in an animal model. Increased arteriolar muscle similar to that seen pathologically in persistent pulmonary hypertension has led some researchers to postulate that long-term exposure to prostaglandin inhibitors could predispose to persistent pulmonary artery hypertension in the newborn. The major agent that has come under scrutiny in this regard is the drug indomethacin. Indomethacin is known to constrict the ductus arteriosus after birth and may lead to closure of this structure postnatally. Anecdotal reports of clinical persistent pulmonary hypertension in neonates after prenatal exposure to aspirin have led to the concern that such drugs are dangerous in pregnancy. On the other hand, large studies of indomethacin or the treatment of preterm labor have shown these drugs to be effective for tocolysis, and the neonatal follow-up has been un-
remarkable. Recent follow-up of the use of indomethacin for preterm labor treatment or palliation of polyhydramnios has shown an incidence of constriction of 2% up to 35%. This phenomenon is reversible with withdrawal of the drug, and there has not yet been a report of a neonatal death attributable to prenatal prostaglandin inhibitor therapy. The finding of prenatal tricuspid valve regurgitation, even

**Figure 4** Fetal lamb ductal constriction. Simultaneous aortic (Ao) and main pulmonary artery (PA) pressure recordings during successively more severe constriction (panels from top to bottom). The instantaneous fetal ductal gradient is obtained by subtraction of the aortic pressure from the pulmonary artery pressure (PA). Note that the diastolic gradient of pressure increases with more severe constriction, as does the simultaneous continuous wave Doppler signal obtained by placing the transducer on the fetal right ventricular outflow tract proximal to the constriction that is created manually by a ligature around the ductus. \( m/s \), Meters per second.
without evidence of ductal constriction, should prompt a search for exposure to prostaglandin inhibitors and may be a marker for later neonatal clinical persistent pulmonary hypertension.11

REFERENCES
