PEDIATRIC CARDIOLOGY

Doppler Echocardiography of Fetal Ductus Arteriosus Constriction Versus Increased Right Ventricular Output

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A prospective longitudinal study from 121 examinations of 41 normal pregnant women showed that fetal ductal flow velocities increased with gestational age. These normal data were compared with data in three groups of fetuses with altered ductal flow velocities: 22 fetuses (mean gestational age 31.3 weeks) had ductal constriction due to maternal indomethacin treatment; 10 fetuses (mean gestational age 27.9 weeks) had been exposed to terbutaline, a positive inotropic agent and 14 fetuses (mean gestational age 33.3 weeks) had hypoplastic left heart syndrome.

In normal fetuses maximal systolic, mean and end-diastolic ductal flow velocities increased linearly ($p < 0.0001$). The pulsatility index did not change (mean $\pm$ 2 SD: 2.46 ± 0.52). Fetuses with ductal constriction had higher maximal, mean and end-diastolic flow velocities and a significantly lower pulsatility index

than did normal fetuses (1.15 ± 0.76; $p < 0.0005$). Six of 10 fetuses of the terbutaline group and 8 of 14 fetuses with hypoplastic left heart syndrome had increased maximal flow velocity, but normal or only mildly elevated mean flow velocity. The pulsatility index in fetuses during terbutaline therapy and with hypoplastic left heart syndrome was significantly higher than in normal fetuses (3.11 ± 0.46 and 3.09 ± 0.7, respectively, vs. 2.46 ± 0.52; $p < 0.0005$).

Fetal ductal waveform analysis was necessary to distinguish fetal ductal constriction from increased right ventricular output. These measurements may be helpful in the diagnosis of left-sided outflow obstruction and assessment of fetal hemodynamic data.

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Doppler echocardiography provides an excellent noninvasive tool for assessing blood flow velocity and pressure gradients across the fetal ductus arteriosus (1). Constriction of the fetal ductus arteriosus may occur during maternal therapy with indomethacin for premature labor (2-4). It has been demonstrated in animals that chronic fetal ductal constriction and occlusion affect the fetal right ventricle and lead to morphologic changes in the pulmonary vasculature, resulting in persistent pulmonary hypertension in the newborn (5-8). Thus, echocardiography of the fetus is used to detect fetal ductal constriction during indomethacin therapy. It has been shown that maximal ductal blood flow velocity increases during weeks 25 to 32 of gestation, but normal values with defined confidence limits are not currently available (1). Furthermore, the fetus whose mother is being

treated with terbutaline to induce tocolysis has increased cardiac output (9); we have noted markedly increased maximal ductal flow velocities in this setting, so increased fetal right ventricular output may simulate ductal constriction.

The aims of this study were 1) to investigate the changes in ductus arteriosus flow velocities during the last 2 trimesters of human gestation, and 2) to compare fetuses with normal versus altered ductus arteriosus flow.

Methods

Normal group. A total of 121 studies were performed on 41 normal pregnant women who were recruited as volunteers from the staff of the Children's Hospital of Philadelphia. The study protocol was approved by the Human Studies Committee and informed consent was obtained from each woman. Fetuses were initially examined after the 14th week of gestation and then at 4 week intervals throughout pregnancy. Women who were taking drugs other than vitamins, or who had complications of pregnancy including premature labor, were excluded. Gestational age was assessed by measurements of biparietal diameter, head circumference, abdominal circumference and femur length (10). All fetuses had a complete postnatal echocardiographic examination within the 1st 3 weeks of postnatal life to exclude congenital heart disease. Gestational age at birth ranged from 38 to 42

weeks (mean 40.4) and birth weight ranged from 3,300 to 5,170 g (mean 3,810).

Ductal constriction group. With use of the criteria of Huhta et al. [1], fetal ductal constriction due to indomethacin therapy for preterm labor was detected in 22 fetuses with a structurally normal heart (gestational age 27 to 34 weeks, mean 31.3) referred from the Department of Obstetrics. All had peak systolic and diastolic flow velocities in the ductus >140 and >30 cm/s, respectively, as previously reported for the gestational age range of 26 to 32 weeks. All women were receiving drug therapy for ≥18 h before the examination. The dose of indomethacin ranged from 100 to 150 mg daily in divided doses. Serial studies demonstrated the change in ductal flow velocity during treatment, but only the examination with the highest flow velocity was used for analysis. Findings of constriction including increased systolic and diastolic flow velocities were present in all fetuses and resolved within 1 to 5 days after discontinuation of indomethacin therapy.

Terbutaline group. Ten fetuses with a structurally normal heart (gestational age 20 to 33 weeks, mean 27.9) were examined while the mothers were being treated for premature labor with terbutaline, 30 mg/day, in 6 doses for ≥24 h before examination. Because of the urgency of treatment, fetuses exposed to terbutaline did not have pretreatment echocardiographic examinations.

Hypoplastic left heart syndrome group. Fourteen fetuses (gestational age 21 to 39 weeks, mean 33.3) were diagnosed in utero as having hypoplastic left heart syndrome, manifested by mitral atresia or stenosis, aortic atresia or stenosis and a hypoplastic aortic arch. Three fetuses had more than one prenatal study. All diagnoses were confirmed by systolic and diastolic reversal in the aortic isthmus on a postnatal echocardiogram [Bash et al. [11]], which showed that the systemic circulation was entirely dependent on the ductus arteriosus, and thus the prenatal ductal flow was equal to the combined cardiac output in these fetuses.

Equipment. An Acuson 128 scanner was used in combination with 5-MHz and 3.5-MHz transducers for all examinations. Doppler interrogations were performed with use of either 5-MHz or 3.5-MHz image-directed continuous wave Doppler echocardiography. The power output was maintained at <100 mW/cm² spatial peak temporal average at all times. Each study was recorded on standard VHS 0.5 in. (1.27 cm) videotape.

Technique. After evaluation of the cardiac anatomy, continuous wave Doppler interrogation of the flow through the ductus arteriosus was performed in a sagittal plane showing the pulmonary artery, ductus arteriosus and descending aorta simultaneously, as previously described [1]. All Doppler recordings were obtained in the absence of fetal breathing movements at an angle of <30° to flow, and color flow mapping was used to align the Doppler beam. Measurements were taken either on-line or off-line from a hard copy of the Doppler tracing with use of a digitizing computer system (Digisonics). An average of 3 beats was used to establish each value. Waveforms were analyzed for maximal, end-diastolic and mean flow velocity, respectively. The pulsatility index was calculated with use of the formula (Maximal velocity − End-diastolic velocity)/Mean velocity.

Statistics. The normal data were analyzed to obtain normal charts with 95% confidence intervals for ductus arteriosus flow velocities during gestation. A simple linear random effects model was used of the form $Y_{ij} = t_i + \beta x_{ij} + e_{ij}$, where Y_{ij} = measured value, t_i = random between-subject variability, βx_{ij} = fixed effect of increasing gestational age and e_{ij} = random within-subject variability. It was assumed that t_i and e_{ij} are independent identically distributed normal random variables, the classic assumptions for random effects models [12]. The pulsatility indexes of the indomethacin and terbutaline groups were compared with values in the normal group using a two-tailed unpaired Student's t test with a significance level at $p < 0.05$. All values are presented as mean values ± 2 SD.

Results

Doppler recordings of the ductus arteriosus flow of fetuses with normal and altered blood flow velocities are shown in Figure 1.

Normal fetuses. From 14 weeks of gestation to term there was a significant increase in maximal systolic, mean and end-diastolic flow velocities ($p < 0.0001$). There was no significant change in the pulsatility index during this period (mean 2.46 ± 0.52).

Fetuses with altered ductus arteriosus flow velocities. Figure 2 compares data in the three groups of fetuses with altered ductus arteriosus flow velocities with data in normal fetuses. The maximal flow velocity was increased above the 95% confidence limits in all fetuses in the group with ductal constriction, in 6 of 10 fetuses in the group affected by terbutaline therapy and in 8 of 14 fetuses in the group with the hypoplastic left heart syndrome. The mean ductal flow velocity was >2 SD in all fetuses with ductal constriction and within the normal confidence limits in all fetuses in the terbutaline group. Four of 14 fetuses with the hypoplastic left heart syndrome had a mean ductal flow velocity slightly above the normal range. The end-diastolic flow velocity was within the normal limits in both the terbutaline and the hypoplastic left heart syndrome group and >2 SD in all fetuses with ductal constriction. Compared with values in normal fetuses, the pulsatility index was significantly lower in fetuses in the ductal constriction group (mean 1.25 ± 0.76; $p < 0.0005$) and significantly higher in fetuses during terbutaline therapy (3.11 ± 0.46; $p < 0.0005$) and in fetuses with the hypoplastic left heart syndrome (3.09 ± 0.7; $p < 0.0005$). There was no significant difference between the pulsatility indexes of the terbutaline and hypoplastic left heart syndrome groups.
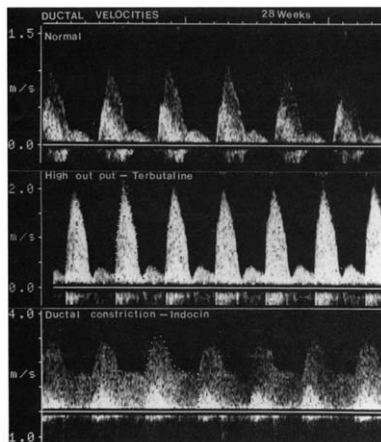
Figure 1. Doppler recordings of fetal ductus arteriosus. Top, normal fetus at 28 weeks of gestation. Middle, fetus at 29 weeks of gestation exposed to terbutaline: there are increased maximal but normal end-diastolic and mean flow velocities (pulsatility index >3). Fetuses with the hypoplastic left heart syndrome have a similar pattern. Bottom, fetal ductal constriction at 31 weeks of gestation with increased maximal, end-diastolic and mean flow velocities (pulsatility index <2).

Discussion

Normal ductal flow velocities. In the 2nd and 3rd trimesters, fetuses showed an increase in ductal flow velocities with increasing gestational age, in agreement with previous data. This increased ductal flow velocity is a function of multiple variables, including ductal diameter and wall compliance, systolic and diastolic ductal flow and right ventricular function. Therefore, flow velocities of the fetal ductus arteriosus must always be related to gestational age for correct interpretation.

Constriction versus increased right ventricular output. Fetal ductal constriction was characterized by increased maximal and diastolic ductal flow velocities, resulting in a Doppler waveform similar to that seen postnatally across coarctation of the aorta (1). In our study, elevated maximal ductal velocity was also found in 60% of the fetuses exposed to terbutaline. Both terbutaline therapy and premature labor have a positive inotropic effect on the fetal heart (9). Increased right ventricular output causes a greater volume of blood to be pumped from the main pulmonary artery to the descending aorta, resulting in an increased maximal ductal flow velocity. The group with increased ductal flow had ductus-dependent hypoplastic left heart syndrome. This lesion can be seen as a model of increased right ventricular output, because the aortic valve was either atretic or severely hypoplastic. We found elevated maximal flow velocities in 57% of these fetuses and the shape of the ductal Doppler waveforms was nearly identical to those seen in fetuses with terbutaline therapy, thus supporting the hypoth-
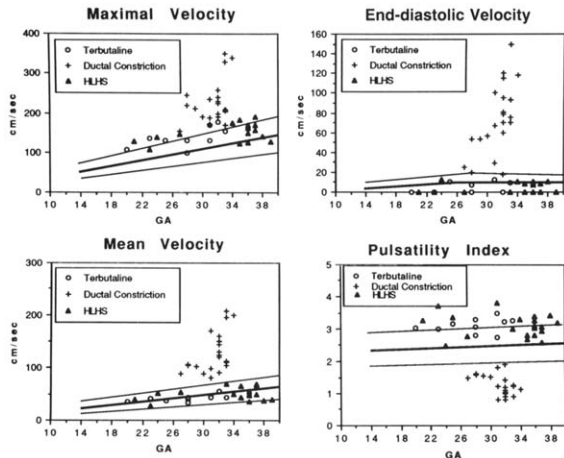

Figure 2. Ductus arteriosus flow velocity and pulsatility index in fetuses exposed to terbutaline (n = 10), fetuses with constriction of the ductus arteriosus (n = 22) and fetuses with the hypoplastic left heart syndrome (HLHS) (n = 14) compared with values in normal fetuses. GA = gestational age in weeks. Heavy and light lines = mean normal values ± 2 SD, respectively.

esis that increased flow volume may cause elevated maximal ductal flow velocity.

When terbutaline therapy fails to stop premature labor, indomethacin is frequently added as a second drug. Increased maximal fetal ductal flow velocity in these cases could be due to indomethacin-induced ductal constriction or the effect of terbutaline-induced increased right ventricular output. If only maximal ductal flow velocity is measured, the latter effect may be misinterpreted as fetal ductal constriction and an effective tocolysis regimen may be discontinued. The shape of the Doppler waveform, however, is different from that seen during ductal constriction. In ductal constriction flow velocity across the ductus arteriosus slowly decreases from its maximum to end-diastole, but increased flow through a wide open ductus arteriosus shows a very pulsatile Doppler pattern, with a rapid decrease after peak velocity to the baseline or near to it, and once again an increase in diastole and a decrease toward end-diastole. This difference in shape can be appreciated by measuring mean flow velocity, or even better, by calculating the pulsatility index, which takes maximal, end-diastolic and mean velocities into account. A flow pattern of a mildly constricted ductus and a wide open ductus with increased flow may have the same maximal systolic and end-diastolic velocities, but there are significant differences in mean velocity and pulsatility index that clearly differentiate each cause. As ductal flow velocities are, to a certain degree, related to right ventricular output, they may be used as part of an assessment of fetal hemodynamic data.

Application to congenital heart disease. Fetuses with the hypoplastic left heart syndrome may have increased maximal ductal flow velocities even early in gestation, and this increase combined with disproportion in the ventricular and great artery sizes may be an additional indicator of fetal left ventricular outflow obstruction and must not be interpreted as ductal constriction.

Constriction of the ductus arteriosus in the normal fetus with two ventricles appears to be well tolerated when it is short-term, and it can be recognized by assessing the ductal flow velocities with Doppler echocardiography. When there is only one pumping chamber, as in the hypoplastic left heart syndrome, the entire cardiac output of the fetus must pass through the ductus arteriosus, and ductal constriction could dramatically increase the work of the right ventricle and decrease the fetal and placental perfusion. For this reason, when premature labor occurs in a woman whose fetus is being monitored for ductus-dependent congenital heart disease, frequent monitoring of the ductal flow velocities is necessary if prostaglandin-inhibiting drugs are to be used. In the setting of postnatal management of the hypoplastic left heart syndrome a cardinal principle is avoidance of myocardial hypertrophy and this principle also applies here.

Pulsatility index as an indicator of obstruction. The pulsatility index in peripheral vessels is thought to reflect peripheral impedance. In the ductus arteriosus it is used only as an aid in the differential diagnosis of increased maximal
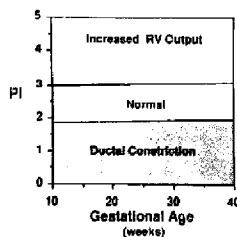

Figure 3. Pulsatility index (PI) of the fetal ductus arteriosus and fetal gestational age. This chart gives the normal range versus the ranges for increased right ventricular (RV) output and ductal constriction.

flow velocity. Ductal constriction causes decreased pulsatility and higher than normal flow velocities indicating obstruction, whereas an increased right ventricular stroke volume causes increased pulsatility and elevated maximal but normal or only slightly elevated mean and end-diastolic flow velocities (Fig. 3). In the umbilical circulation, for example, decreased pulsatility is at low velocity, indicating increased flow and lower impedance (13). Mean ductal flow velocity alone may be able to distinguish ductal constriction from other causes of elevated maximal flow velocity, but it must be interpreted in relation to gestational age. Pulsatility index, in contrast, did not change with gestational age and may therefore be a more useful variable in clinical practice.

Conclusions. Fetal ductal waveform analysis is necessary to differentiate fetal ductal constriction and increased fetal right ventricular output. The mean flow velocity and the pulsatility index are the most useful variables in the analysis of Doppler waveforms. These measurements may be helpful in the diagnosis of left-sided outflow obstruction and assessment of fetal hemodynamics.

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