Morphological and Physiological Predictors of Fetal Aortic Coarctation

Hikoro Matsui, MD; Mats Mellander, PhD, MD; Michael Roughton, PhD; Hana Jicinska, MD; Helena M. Gardiner, PhD, MD

Background—Prenatal diagnosis of aortic coarctation suffers from high false-negative rates at screening and poor specificity.

Methods and Results—This retrospective study tested the applicability of published aortic arch and ductal Z scores (measured just before the descending aorta in the 3-vessel and tracheal view) and their ratio on 200 consecutive normal controls at a median of 22 and 0 gestational weeks (range, 15 and 4 to 38 and 4 weeks). Second, this study tested the ability of serial Z scores to distinguish fetuses with coarctation within a cohort with ventricular and/or great arterial disproportion detected at screening or fetal echocardiography. Third, it evaluated the diagnostic significance of associated cardiac lesions, coarctation shelf, and isthmal flow disturbance. We studied 44 fetuses with suspected coarctation at 24 and 0 weeks (range, 17 and 3 to 37 and 4 weeks). Receiver-operating characteristic curves were created. Logistic regression tested the association between z scores, additional cardiac diagnoses, and coarctation. Good separation was found of isthmal Z scores for cases requiring surgery from controls and false-positive cases, and receiver-operating characteristic curves showed an excellent area under the curve for isthmal Z score (0.963) and isthmal-to-ductal ratio (0.969). Serial isthmal Z scores improved to in suspected cases with normal outcomes; those requiring surveillance or surgery remained in. Minor lesions did not increase the diagnostic specificity of coarctation, but isthmal flow disturbance increased the odds ratio of true coarctation versus arch hypoplasia 16-fold.

Conclusions—Isthmal Z scores and isthmal-to-ductal ratio are sensitive indicators of fetal coarctation. Serial measurements and abnormal isthmal flow patterns improve diagnostic specificity and may reduce false positives. (Circulation. 2008; 118:1793-1801.)

Key Words: coarctation | fetus | pediatrics

Coarctation of the aorta is the most common duct-dependent cardiac defect missed at routine physical screening of the neonate.1 An estimated 60% to 80% of newborns with isolated coarctation are sent home as “healthy” babies,1-3 to face circulatory collapse and death as the duct closes or, if closure is gradual, prostaglandin rescue and surgery.

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Diagnostic difficulties occur at antenatal screening, where a high false-negative rate is present, and at the hands of the fetal cardiologist. Current echocardiographic methods seem unable to reduce the high false-positive rate of diagnoses among those referred from screening programs.

Prenatal diagnosis improves survival and reduces morbidity4,5 by allowing planned delivery in a tertiary center and early institution of prostaglandin treatment to prevent ductal constriction, but this ideal is rarely achieved, and only 19% of admissions to a large cardiac center for left-sided obstruction have had an antenatal diagnosis.6 More comprehensive information is obtained from unselected populations. In 1 regional study, only 6% of babies born with arch obstruction had an antenatal diagnosis, and half of the neonates requiring cardiac surgery for all types of malformations were diagnosed only after discharge from hospital when they became symptomatic.3 It is recognized that not all cases of arch obstruction develop in the neonatal period and that, in an unknown proportion, hypoplasia of the arch may progress to coarctation of the aorta, requiring surgery or interventional catheter in infancy or childhood. Thus, coarctation is one of the most difficult cardiac defects to screen for and diagnose before birth. Suspicion of coarctation is raised by the finding of disproportion at the 4-chamber and/or 3-vessel and tracheal views at screening. Although coarctation of the aorta is high in the differential diagnosis of cardiac disproportion, the sensitivity and positive predictive power of ventricular dis-
proportion recognized at screening are low, at \( \approx 62\% \) and 33\%, respectively.\(^7\)\(^8\) The differential diagnosis of isolated 4-chamber cardiac disproportion is varied but includes cardiovascular diagnoses such as vein of Galen aneurysm and noncardiac diagnoses such as aneuploidy, anemia, and growth restriction caused by placental insufficiency. These noncardiac causes should be investigated by fetal medicine specialists. Once a cardiac diagnosis is suspected and the fetus is referred to a fetal cardiologist, the false-positive rate is 20\% to 30\%, rising to 80\% in 1 report.\(^7\)\(^–\)\(^9\)

In view of the devastating perinatal course following a missed diagnosis of coarctation of the aorta, it is important to improve detection at obstetric screening and to reduce the number of false-negative cases.\(^10\) To achieve this objective, we have trained sonographers to incorporate the 3-vessel and tracheal view into their routine screening so that they can visually recognize great arterial disproportion, which is an abnormal finding in the first- and second-trimester fetus.\(^11\) To enable serial objective quantification of the degree of hypoplasia present in the aortic arch, we have published Z scores calculated as previously described by our group\(^12\) (Figure 1). In our original report, the results were presented as Z scores related to gestational age and femoral length. In the present study, we used gestational-age Z scores because we found no significant difference between these and femoral-length Z scores, and their use allowed comparison with our retrospective normal cases in whom femoral length was not necessarily available on the same day.

**Methods**

**Control Group**

The first 200 consecutive singleton fetuses referred during 2004 for cardiac scan and found to have normal cardiac anatomy were chosen to test the applicability of our Z scores to the general fetal population. The fetuses were scanned at a median of 22\(\pm\)4 weeks gestation. We checked for these fetuses in the national Congenital Cardiac Audit Database, which lists all cardiac surgical and catheter interventions; none had developed coarctation of the aorta during the year after delivery. The measurements were made by a single investigator (H.M.) from the archived recordings of the fetal echocardiograms. The diameters of the aortic isthmus and duct were measured in the 3-vessel and tracheal view immediately before their entry into the descending aorta, and the Z scores and isthmal-to-ductal-diameter ratio were calculated as previously described by our group\(^12\) (Figure 1). In our original report, the results were presented as Z scores related to gestational age and femoral length. In the present study, we used gestational-age Z scores because we found no significant difference between these and femoral-length Z scores, and their use allowed comparison with our retrospective normal cases in whom femoral length was not necessarily available on the same day.

**Study Group**

All pregnant women referred for specialist fetal echocardiography and found to have ventricular and/or arch disproportion during the period of January 2000 to December 2005 were eligible for inclusion in the study. Their echocardiograms were analyzed retrospectively by an investigator (H.M. or H.J.) blinded to outcome.

The diagnosis of disproportion was subjective and suspected visually. No chamber sizes were measured. In practice, disproportion was noticeable when an \( \approx 20\% \) difference was found in ventricular widths or in the transverse portion of the ductal and aortic arches.

Only fetuses suspected of having isolated coarctation (ie, normal situs, concordant atrioventricular and ventriculoarterial connections, and a biventricular atrioventricular connection) were included. Forty-eight fetuses fulfilled these inclusion criteria. Two were excluded because of incomplete outcome data, and another 2 were enrolled but later excluded because the pregnancy was terminated. Thus, the study comprised 44 fetuses with suspicion of coarctation in whom outcome was known until at least 1 year of age. Minor secondary diagnoses of atrial or ventricular septal defect, bicuspid aortic valve, and persistent left superior caval vein to coronary sinus were identified; their frequency is presented in Table 1. The arch

![Figure 1. Magnification of the 3-vessel and tracheal view showing the pulmonary trunk (PA) leading into the arterial duct (D). The isthmus (I) is measured as shown by the line just before it enters the descending aorta and the duct measured opposite it (line). L indicates left; R, right; and Ao, aorta.](image)

### Table 1. Secondary Diagnoses in Fetuses Referred With Suspected Aortic Coarctation

<table>
<thead>
<tr>
<th>Factor</th>
<th>Surgery (n=20), n (%)</th>
<th>Surveillance (n=7), n (%)</th>
<th>Postnatal Normal (n=17), n (%)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shelf</td>
<td>9 (45)</td>
<td>0 (0)</td>
<td>1 (6)</td>
<td>0.005</td>
</tr>
<tr>
<td>Flow disturbance</td>
<td>13 (65)</td>
<td>1 (14)</td>
<td>0 (0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Shelf and flow disturbance</td>
<td>6 (30)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0.015</td>
</tr>
<tr>
<td>Flow disturbance, no shelf</td>
<td>7 (35)</td>
<td>1 (14)</td>
<td>0 (0)</td>
<td>0.022</td>
</tr>
<tr>
<td>VSD</td>
<td>10 (50)</td>
<td>3 (43)</td>
<td>2 (12)</td>
<td>0.044</td>
</tr>
<tr>
<td>LSVC</td>
<td>4 (20)</td>
<td>4 (57)</td>
<td>7 (41)</td>
<td>0.149</td>
</tr>
<tr>
<td>Bicuspid AoV</td>
<td>5 (25)</td>
<td>0 (0)</td>
<td>1 (6)</td>
<td>0.125</td>
</tr>
</tbody>
</table>

VSD indicates ventricular septal defect; LSVC, left superior vena cava; and AoV, aortic valve.
views were examined for the presence of tissue in the posterior part of the arch on sagittal view (a coarctation shelf) (Figure 2A and 2B) and the presence of continuous flow at the isthmus on either the 3-vessel and tracheal or sagittal view (Figure 2C). The median age at referral was 24±0 gestational weeks (range, 17±3 to 37±4 weeks).

From the case notes, we reviewed our opinion (written at the first examination) and classified the case as highly likely, possibly, or unlikely to have coarctation. Because this is a retrospective study, the postnatal outcome is known, and each case is classified as “surgery” (requiring surgery for coarctation), “surveillance” (because arch hypoplasia was present and coarctation could not be definitely excluded), or “postnatal normal” (antenatally suspected at screening but a definitely normal arch after ductal closure). Because none of the cases in the surveillance group developed arch obstruction requiring surgery, we have considered them to be false-positive diagnoses of coarctation in our subsequent analyses.

Ethical Considerations
We discussed this study with the institutional review board, but specific ethical approval was not necessary because the sonographic measurements were performed as an integral part of routine clinical visits for which informed consent from the patients is a part.

Statistical Analysis
Z scores were created using natural logarithms in a 2-stage process as described previously. We assigned gestational age on the basis of completed weeks of gestation: predicted isthmal or ductal diameter=ln[predicted isthmal or ductal diameter]=m ln(gestational age)+c, and Z score=[ln(measured isthmal or ductal diameter)−ln(predicted isthmal or ductal diameter)]/root MSE, where m and c are the slope and intercept, respectively, of the regression equations used to predict the cardiac dimensions on the basis of the measured values of gestational age and MSE is mean squared error.

Cross-sectional scores were calculated from the 200 control fetuses and serial Z scores for all but 3 cases of suspected coarctation that attended only once. Receiver-operating characteristic curves were created for measurements of the isthmal and ductal diameters and their ratio from the first examination. Logistic regression was used to test the association between the Z scores, additional cardiac diagnoses, and coarctation. When serial scans were used from the same fetus, a multilevel logistic regression model was used, with the fetus declared as a random effect. Within the multilevel model, an independent variance structure was used, with a unique variance estimate associated with each subject and no between-subject covariances. Multivariable analysis was used to assess the interdependence of significant variables. All analyses were repeated using only scans taken in the third trimester (from >26 weeks’ gestation) to see whether their use improved prediction of the requirement for postnatal surgery. The κ value was used to test agreement between the clinical impression (assigned without making measurements) and postnatal outcome.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Study Group
One of the 44 babies had an extracardiac malformation (multicystic kidney), and 3 had a chromosomal defect (Turner

Figure 2. A, Discrete coarctation shelf seen in the aorta of a 27-week-gestation fetus. B, Postmortem specimen of the same fetus born at 38 weeks demonstrating coarctation shelf (baby died of laryngeal atresia with tracheoesophageal fistula). C, Continuous low-velocity Doppler waveform resulting from the obstruction of flow at the isthmus. AsAo indicates ascending aorta; DsAo, descending aorta.
syndrome, 45XO in 2 diagnosed antenatally; trisomy 13 in 1 confirmed after preterm delivery). Twenty of the 44 fetuses with ventricular or great arterial disproportion had coarctation of the aorta; 19 had surgery. The diagnosis of coarctation was confirmed at postmortem for the baby with trisomy 13. Seven babies had long-segment arch hypoplasia and were kept under surveillance to exclude the development of coarctation during the first year; they are considered false-positive diagnoses. The remaining 17 infants had sonographically normal appearances of the aortic arch and were discharged home only after the duct had closed in accordance with our usual practice for management of cases suspected antenatally to be at risk for coarctation. No case has required surgery later than the perinatal period.

Identification of Abnormality

The aortic arch Z scores and the isthmal-to-ductal ratio enabled good separation between the 200 fetuses in the control group and those with disproportion suspected to have coarctation at the first scan (Figure 3A and 3B). The Z scores demonstrated less variance in our control population than in the population used to derive the scores, which may be explained by the use of a single examiner in this study. We have described that the normal isthmal-to-ductal ratio approaches 1 with a 95% reference range of 0.74 to 1.23 and does not change significantly in the normal fetal population during the second and third trimesters. Of the 44 fetuses in the study group, 40 had an isthmal-to-ductal ratio at first examination <0.74, and this included all 27 fetuses who required postnatal surgery or surveillance. In contrast, the 4 fetuses with ratios in the normal range were all normal after delivery.

Receiver-operating characteristic curves were used to test the ability of isthmal and ductal Z scores and the isthmal-to-ductal ratio to differentiate between normal outcomes (controls, postnatal normal, and surveillance groups; n=224) and cases requiring surgery (20 babies). The isthmal and ductal Z scores showed an excellent area under the curve for the first scan of 0.963 (95% confidence interval [CI], 0.940 to 0.985) and 0.969 (95% CI, 0.949 to 0.990), respectively, whereas measurements of the ductal-diameter Z scores alone were less powerful at 0.726 (95% CI, 0.571 to 0.881; Figure 4).
Refining the Diagnosis: Serial Measurements, Isthmal Morphology, and Flow Disturbance

At the first scan, the isthmal-to-ductal ratio of 4 cases of suspected coarctation lay above the lower 95% CI. All proved to be normal after delivery (Figure 5A). The isthmal Z scores of 21 fetuses with disproportion were ≥2 and thus lay within the normal range (Figure 5B). Eight required surgery for coarctation of the aorta; 2 were kept under surveillance; and 11 were considered normal after the duct closed. The serial isthmal-to-ductal ratios and isthmal Z scores are shown in Figure 6A and 6B. Those who proved normal postnatally showed an improvement in the ratio or Z score to within the normal ranges during pregnancy but remained below the lower limit of normal or worsened for both parameters in all but 2 of those requiring surgery and 3 kept under surveillance after birth; their isthmal Z scores remained in the low-normal range (Figure 6B). Thus, serial isthmal Z scores and isthmus-to-ductal ratios could distinguish those who would require surgery from those requiring surveillance with odds ratios (ORs) of 0.52 (95% CI, 0.320 to 0.847) and 0.92 (95% CI, 0.869 to 1.052), respectively (Table 2). The higher (less negative) the scores were, the less likely it was that a true coarctation of the aorta existed.

The correlation of the within-subject measurements was reasonably high. Of the 44 patients with suspected coarctation of the aorta, the intra-class correlation coefficient for the isthmus Z scores, ductal Z scores, and isthmal-to-ductal ratio were 0.75, 0.44, and 0.71, respectively. For the cases with confirmed coarctation of the aorta, the intra-class correlation coefficient values were 0.65, 0.50, and 0.63.

Very little difference was found in the area under the receiver-operating characteristic curves created using the first scan only against using all available serial scans. The serial scans showed a marginal decrease in the area under the curve: Isthmal Z scores decreased from 0.963 to 0.958 \( (P=0.93) \); the isthmal-to-ductal ratio decreased from 0.969 to 0.965 \( (P=0.94) \); and ductal Z scores decreased from 0.726 to 0.654 \( (P=0.25) \).
In addition to growth of the aortic and ductal arches, we analyzed whether visualization of a posterior shelf and/or flow disturbance at the isthmus could increase the cardiologist’s ability to predict whether a fetus would require surgery for coarctation of the aorta in the neonatal period (Table 3). All were independent predictors of surgery. Multivariable logistic regression showed that the presence of flow disturbance at the isthmus increased the chances of a true coarctation 15.8-fold in this fetal cohort with cardiac disproportion.

**Identification of Abnormality Using Scans at >26 Weeks’ Gestation Only**

Because serial scans seemed to help distinguish suspicious cases that proved normal after birth from those requiring surgery or surveillance, we analyzed separately the measurements made in the third trimester after 26 weeks. These measurements were as good in separating control cases from those requiring surgery and were useful in separating those requiring surgery from those requiring surveillance (isthmus Z scores: OR, 0.312; 95% CI, 0.138 to 0.706; \( P = 0.005 \); isthmal-to-ductal ratio: OR, 0.894; 95% CI, 0.826 to 0.967; \( P = 0.005 \)).

**Likelihood of Coarctation of the Aorta: Additional Echocardiographic Features**

The frequency of minor secondary diagnoses such as ventricular septal defect, bicuspid aortic valve, and persistent left superior caval vein to coronary sinus, as well as the presence of a coarctation shelf and flow disturbance in the isthmus, also was documented prospectively (Table 1). Logistic regression showed that the presence of flow disturbance increased the OR for coarctation 22-fold (95% CI, 4.5 to 103; \( P = 0.001 \)), a ventricular septal defect increased it slightly to 1.4 (95% CI, 0.5 to 4; \( P = 0.52 \)), and the presence of a left superior caval vein reduced the OR to 0.3 (95% CI, 0.1 to 1.0; \( P = 0.05 \)). When a shelf was visualized, surgery was required in all but 1, who proved normal postnatally.
Likelihood of Coarctation of the Aorta: 
Clinical Impression
The degree of agreement between the fetal cardiologist’s first 
clinical impression and outcome was 77%, with a \( \kappa \) value of 0.63 (Table 4). Nineteen of the 24 classified as highly likely 
to have coarctation of the aorta at the first scan required 
surgery, and all 12 thought unlikely to have coarctation were 
normal. The remaining 8 fetuses classified as possibly having 
coarctation had a mixed outcome: 1 had surgery for coarcta-
tion, 3 required surveillance for arch hypoplasia; and 4 were 
normal.

Discussion
Aortic coarctation is one of the most poorly detected lesions 
at routine prenatal and postnatal screening and is life-
threatening if undiagnosed.1–3,6,14 It is important to develop 
better screening methods both before and after birth. Arch 
obstruction occurs in the fetus; it is not a postnatal event but 
a dynamic situation in the fetus.10 In this unselected series 
of fetuses with disproportion, we have demonstrated a posterior 
shelf and flow disturbance at the isthmus in 45% and 65% 
cases of true coarctation of the aorta, respectively. Moreover, 
these were specific signs of coarctation, each occurring in 
only 1 case that did not require neonatal surgery, giving a 
specificity of 90% and 94%, respectively. Fetuses who had 
flow obstruction were 15.8-fold more likely to require sur-
gery for coarctation of the aorta after birth than those with 
arch hypoplasia. Because all but 1 with a shelf required 
surgery, we could not calculate an OR to distinguish those 
requiring surgery from surveillance.

Redistribution of flow at the atrial level from left to right is 
1 explanation for disproportion at the 4-chamber and arch 
views, but growth velocities may alter during gestation and 
permit sufficient arch growth to avoid surgery. These babies 
are often born with arch hypoplasia, and late coarctation has 
been described.15 Four-chamber disproportion may be subtle, 
and disproportion may be visible only at the arch views. 
Therefore, screening using the 3-vessel and tracheal view is 
important to avoid false-negative results. We also recommend 
this view to fetal cardiologists because color velocity and 
energy enhance disproportion and may reveal a holdup of 
flow at the isthmus, which further increases specificity of 
diagnosis. Current specificity of diagnosis is poor, and the 
high false-positive rates of up to 81% reported by fetal 
cardiologists reviewing suspected cases in tertiary referral 
centers reflect the cautious postnatal management plan insti-

Table 2. ORs for Coarctation Using Z Scores of Aortic Isthmus, 
Arterial Duct, and Ratio of Isthmal to Ductal Diameters for All 
Gestational Ages

<table>
<thead>
<tr>
<th>Measurement</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical cases vs controls and false-positive cases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All scans used</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isthmal Z score (GA)</td>
<td>0.008</td>
<td>0.000–0.170</td>
<td>0.002</td>
</tr>
<tr>
<td>Ductal Z score (GA)</td>
<td>2.434</td>
<td>1.624–3.648</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Isthmal-to-ductal ratio×100</td>
<td>0.792</td>
<td>0.724–0.866</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Only first scan used</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isthmal Z score (GA)</td>
<td>0.234</td>
<td>0.148–0.369</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ductal Z score (GA)</td>
<td>4.709</td>
<td>2.416–9.177</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Isthmal-to-ductal ratio×100</td>
<td>0.876</td>
<td>0.836–0.917</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Need for surgery vs surveillance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All scans used</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isthmal Z score (GA)</td>
<td>0.521</td>
<td>0.320–0.847</td>
<td>0.009</td>
</tr>
<tr>
<td>Ductal Z score (GA)</td>
<td>1.258</td>
<td>0.711–2.224</td>
<td>0.430</td>
</tr>
<tr>
<td>Isthmal-to-ductal ratio×100</td>
<td>0.920</td>
<td>0.869–0.973</td>
<td>0.004</td>
</tr>
<tr>
<td>Only first scan used</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isthmal Z score (GA)</td>
<td>0.781</td>
<td>0.362–1.685</td>
<td>0.529</td>
</tr>
<tr>
<td>Ductal Z score (GA)</td>
<td>1.101</td>
<td>0.440–2.757</td>
<td>0.837</td>
</tr>
<tr>
<td>Isthmal-to-ductal ratio×100</td>
<td>0.962</td>
<td>0.878–1.052</td>
<td>0.395</td>
</tr>
</tbody>
</table>

GA indicates gestational age.

Table 3. Factors Predictive of Surgery for Aortic Coarctation

<table>
<thead>
<tr>
<th>Measurement</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Need for surgery vs surveillance</td>
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<td></td>
<td></td>
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<tr>
<td>Isthmal Z score (GA)</td>
<td>0.521</td>
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<td>0.009</td>
</tr>
<tr>
<td>Ductal Z score (GA)</td>
<td>1.258</td>
<td>0.711–2.224</td>
<td>0.430</td>
</tr>
<tr>
<td>Isthmal-to-ductal ratio×100</td>
<td>0.920</td>
<td>0.869–0.973</td>
<td>0.004</td>
</tr>
<tr>
<td>Flow disturbance</td>
<td>21.706</td>
<td>...</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VSD</td>
<td>1.407</td>
<td>0.490–4.043</td>
<td>0.526</td>
</tr>
<tr>
<td>LSVC</td>
<td>0.349</td>
<td>0.121–1.002</td>
<td>0.050</td>
</tr>
<tr>
<td>Multivariable analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isthmal-to-ductal ratio×100</td>
<td>0.946</td>
<td>0.888–1.008</td>
<td>0.085</td>
</tr>
<tr>
<td>Flow disturbance</td>
<td>15.860</td>
<td>...</td>
<td>0.001</td>
</tr>
</tbody>
</table>

VSD indicates ventricular septal defect; LSVC, left superior vena cava.

Table 4. Agreement Between the Clinical Impression of the 
Fetal Cardiologist After the First Scan and the Postnatal 
Outcome

<table>
<thead>
<tr>
<th>Clinical Grading</th>
<th>Surgery</th>
<th>Surveillance</th>
<th>Postnatal</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highly likely coarctation</td>
<td>19</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Possibly coarctation</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Unlikely coarctation</td>
<td>0</td>
<td>0</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>

Observed agreement, 77.3%. \( \kappa = 0.63 \) (95% CI, 0.42 to 0.85).
It is assumed that in most centers once antenatal suspicion is raised. Although this was warranted in view of the severity of the disease if undiagnosed, transfer of place of delivery to a tertiary center and admission to a cardiac unit for surveillance pending closure of the arterial duct are expensive and may be difficult for the family. Poor specificity was confirmed in our study, in which the accuracy of our clinical impression in predicting the need for postnatal arch repair or surveillance was 77% for cases thought either highly likely or highly unlikely to be coarctation but only 50% in borderline cases referred with disproportion. If one considers a true positive to be a case requiring surgery in the perinatal period and not to include those requiring surveillance for arch hypoplasia (cases we believe are important to identify and monitor), the true-positive rate (based on our usual observations and not these study measurements) was 62.5%. We believe this study has identified more objective measurements that will assist us in risk stratification of those suspected to have coarctation at screening in the future.

Screening for Fetal Coarctation

The proportion of neonates admitted to our pediatric cardiac surgical unit last year with coarctation of the aorta requiring surgery who had an antenatal diagnosis of isolated coarctation (as defined in Methods) was 32%, which is better than the 19% reported from other cardiac centers or the 6% antenatal detection rate described in a regional UK study. This is similar to the proportion admitted for surgery with an antenatal detection of ventriculoarterial discordance (simple transposition of the great arteries, 38%) and tetalogy of Fallot (35%). This suggests that our training strategy is beginning to achieve success in reducing the false-negative rate within the screening programs in our referral area. Most referring obstetric units now screen the fetal heart in 5 transverse views, including the 3-vessel and tracheal view, in the second trimester. They form a visual appreciation of the relative sizes of the aortic and ductal arches (without making measurements) and refer if the arches are not equivalent in size, if the aortic arch is right sided, or if a persistent left superior caval vein is identified. Disproportion of the arch vessels identifies a population of fetuses at risk of coarctation (or interrupted aortic arch), and increased detection of isolated coarctation is reported in some screening programs as a result of similar training initiatives.

Incorporation of the 3-vessel and tracheal view into screening will identify more cases of persistent left superior caval vein with or without 4-chamber disproportion. We and others have published our early observations on the coexistence of a persistent left superior caval vein and congenital heart disease and extracardiac malformations in the fetus. In our previous study, we found that it increased the odds of congenital heart disease to 8.43 and was seen in half of the cases of coarctation requiring surgery. We have included the fetuses from this early experience in this study. In our current cohort, half of the fetuses with a persistent left superior caval vein did not have coarctation or arch hypoplasia after birth, and its detection decreased the likelihood of requiring surgery for coarctation to 0.35. This is in agreement with the findings of others who have reported that, although it is seen more commonly in association with congenital heart disease and important extracardiac malformations such as the CHARGE syndrome or esophageal atresia than in the normal population, the enlarged coronary sinus may lead to 4-chamber disproportion and may increase false-positive diagnoses of coarctation at screening.

Applicability of Z Scores to the General Fetal Population

In the present study, we tested our previously developed Z scores derived from measurements of the diameters of the distal aortic isthmus and arterial duct in another population of normal fetuses to assess its general applicability and then in a cohort at risk of coarctation resulting from ventricular or great arterial disproportion. These measurements achieved good separation of the cohort with true coarctation of the aorta from the normal population at the first scan.

Gestational Age at Screening

Earlier gestational age at first examination is known to improve the specificity of diagnosis of coarctation. This was confirmed in our study in which 3 fetuses seen for the first time after 32 gestational weeks (and on only 1 occasion) showed lack of agreement between clinical impression and outcome. However, the predictive power of our serial Z scores and ratios was as good when data recorded only after 26 weeks were analyzed (Table 2). The use of serial isthmal Z scores and the absence of a shelf or flow disturbance in the isthmus would have been helpful in deciding that these 3 cases were true negatives.

Study Limitations

Our study was not designed to test the sensitivity and specificity of the measurement of isthmus diameter (alone or related to duct diameter) in a large unselected population of fetuses as part of a screening program but to explore factors that might improve specificity once a diagnosis was suspected. Although these measurements are relatively simple and reproducible in the hands of an experienced fetal cardiologist, we are not recommending their routine use at screening of the low-risk population by sonographers because of time constraints. We believe that the 3-vessel and tracheal view can be used to visually identify fetuses with arch disproportion, thus increasing the sensitivity of screening.

Although 5 of 6 fetuses with proven bicuspid aortic valve had true coarctation of the aorta, we could not confirm a predictive association statistically because of insufficient power in the study. A larger series may confirm this, but antenatal diagnosis of bicuspid aortic valve is not always reliable. The CIs for multivariable logistic regression of flow disturbance at the isthmus were wide, reflecting the small sample size, and have been omitted from Table 3.

In late gestation, the isthmal-to-ductal ratio may be low as a result of ductal dilatation owing to a restrictive oval foramen that causes right-sided enlargement and may reduce the utility of this ratio used in isolation in advanced gestational age.

Conclusions

Fetal arch obstruction is a dynamic process in which obstruction exists in the setting of rapid fetal growth. Improved
sensitivity of coarctation at screening is possible by including transverse views of the aortic and ductal arches routinely and referring if disproportion is seen. Our first arch Z scores and the isthmal-to-ductal diameter ratio were able to separate fetuses at risk of coarctation from normal fetuses but could not reduce false-positive diagnoses. However, diagnostic specificity was improved by serial Z score and ratio measurements; it was improved 15.8-fold if a flow disturbance in the isthmus was detected. The presence of a shelf also was an excellent indicator of coarctation. We recommend early postnatal surveillance until the duct has closed, even in cases exhibiting good prenatal growth of the isthmus, until more experience has been gained with these indices.

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Disclosures
None.

References

CLINICAL PERSPECTIVE
Undiagnosed coarctation can cause neonatal circulatory collapse and death, but morbidity is reduced by antenatal detection and appropriate perinatal management. Identification of isolated coarctation at obstetric screening is notoriously difficult; one 20-year regional series reported that only 6% of isolated coarctation was detected antenatally. Fetal coarctation is suspected sonographically from disproportion at 4-chamber or great arterial views. Incorporating the 3-vessel and tracheal view into obstetric screening programs enables assessment of the relative sizes of aortic and ductal arches and may reduce false-negative diagnoses, but surveillance of false-positives cases, estimated at ~30%, incurs hospital costs. This article analyzes the ability of measurements and Doppler in the arches to improve diagnostic specificity. We report that the receiver-operating characteristic curves of isthmal Z scores and the isthmal-to-ductal ratio can identify cases requiring surgery at first examination and that serial measurements allow separation of normal arches from those requiring surgery or observation during infancy. Continuous isthmal Doppler flow increased the likelihood ratio of coarctation 16-fold, and visualization of a coarctation shelf was specific for those requiring surgery. Ventricular septal defect and bicuspid aortic valve were seen in 50% and 25% of true coarctation, respectively, but did not increase the specificity of diagnosis, and left superior vena cava generated false-positive cases. False-negative diagnoses of coarctation may be reduced by appreciating arch disproportion at obstetric screening using the 3-vessel and tracheal view, and false-positive diagnoses can be reduced in the tertiary center by serial measurements and detection of isthmal flow disturbance or coarctation shelf.