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Clinical Research

Improving Prenatal Diagnosis of Coarctation of the Aorta

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ABSTRACT

Background: The purpose of the study was to evaluate the association between fetal echocardiographic measurements and the need for intervention (primary coarctation repair, staged coarctation repair, or catheter intervention) in prenatally diagnosed coarctation of the aorta.

Methods: A single-centre retrospective cohort study (2005-2015) of 107 fetuses diagnosed with suspected coarctation of the aorta in the setting of an apex-forming left ventricle and antegrade flow across the mitral and aortic valves.

Results: Median gestational age at diagnosis was 32 weeks (interquartile range, 23-35 weeks). Fifty-six (52%) did not require any neonatal intervention, 51 patients (48%) underwent a biventricular repair. In univariable analysis, an increase in ascending aorta (AAo) peak Doppler flow velocity (odds ratio [OR], 1.40 [95% confidence interval [CI], 1.05-1.91] per 20 cm/s; $P = 0.03$) was associated with intervention. No intervention was associated with larger isthmus size (OR, 0.23; $P < 0.001$), transverse arch diameter (OR, 0.23; $P < 0.001$), and aortic (OR, 0.72; $P = 0.02$), mitral (OR, 0.58; $P = 0.001$), and AAo (OR, 0.53; $P < 0.001$) z-scores. In multivariable analysis, higher peak AAo Doppler (OR, 2.51 [95% CI, 1.54-4.58] per 20 cm/s; $P = 0.001$) and younger gestational age at diagnosis (OR, 0.81 [95% CI, 0.70-0.93] per week; $P = 0.005$) were associated with intervention,

RÉSUMÉ

Contexte : Cette étude visait à évaluer le lien entre les données obtenues à l'échocardiographie fœtales et la nécessité d'intervenir (réparation d'une coarctation native, réparation par étapes de la coarctation ou cathétérisme interventionnel) dans les cas de coarctation de l'aorte diagnostiquée avant la naissance.

Méthodologie : Étude de cohorte rétrospective (2005-2015) monocentrique menée chez 107 fœtus soupçonnés de coarctation de l'aorte en dépit du fait que l'apex du cœur est bien formé par le ventricule gauche et que les flux aortique et mitral sont antérogrades.

Résultats : L'âge gestationnel médian au moment du diagnostic était de 32 semaines (intervalle interquartile : de 23 à 35 semaines). Cinquante-six (52 %) nouveau-nés n'ont pas nécessité d'intervention néonatale, mais 51 patients (48 %) ont dû subir une réparation biventriculaire. L'analyse unidimensionnelle a mis au jour un lien entre la réalisation d'une intervention et une augmentation de la vitesse maximale du flux sanguin au niveau de l'aorte ascendante objectivée par écho-Doppler (risque relatif approché [RRA] : 1,40 [intervalles de confiance (IC) à 95 % : de 1,05 à 1,91] par 20 cm/s; $p = 0,03$). L'absence d'intervention était corrélée aux diamètres les plus larges de l'isthme (RRA : 0,23; $p < 0,001$) de l'aorte transversale de la crosse de l'aorte de plus grand diamètre (RRA : 0,23; $p < 0,001$), de l'anneau

Aortic coarctation accounts for 5%-7% of all forms of congenital heart disease,[1,2] and is one of the most difficult to detect at prenatal screening[3] with previously reported true positive detection rates of < 50%.[4-7] In addition, there is a high false positive rate, which might result in unnecessary perinatal precautions, such as altering the delivery location late in pregnancy, recommending the use of prostaglandins, and lengthy hospitalization for observation.[8] A prenatal diagnosis of aortic coarctation is challenging but important because early detection reduces mortality and morbidity.[9] Isthmal hypoplasia, transverse arch hypoplasia, presence of a ventricular septal defect (VSD) and a hypoplastic aortic valve are known risk factors for coarctation but their ability to predict surgery has been reported as low as 65%.[8,10-14] The challenge prenatally is to distinguish between patients with right ventricular (RV) to left ventricular (LV) disproportion, abnormal 3-vessel view, hypoplastic transverse arch, or isthmus who will be normal after birth from those with true coarctation requiring intervention.

The purpose of this study was therefore to determine whether there are any novel prenatal echocardiographic variables in cases with suspected coarctation that are associated with true coarctation requiring neonatal intervention.

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whereas a higher AAo z-score (OR, 0.65 [95% CI, 0.43-0.94] per z; $P = 0.029$) and transverse arch dimension (OR, 0.44 [95% CI, 0.18-0.97]; $P = 0.05$) decreased the risk of intervention.

Conclusions: In prenatally suspected coarctation, the variables associated with intervention comprised smaller AAo and transverse arch size, earlier gestational age at diagnosis, and the additional finding of a higher peak AAo Doppler.

aortique (RRA : 0,72; $p = 0,02$), de l'anneau mitral (RRA : 0,58; $p = 0,001$) et de l'aorte ascendante (RRA : 0,53; $p < 0,001$). L'analyse multivariée a permis d'établir un parallèle entre l'intervention et une vitesse maximale plus élevée du flux sanguin au niveau de l'aorte ascendante objectivée par écho-Doppler (RRA : 2,51 [IC à 95 % : de 1,54 à 4,58] par 20 cm/s; $p = 0,001$) et un plus jeune âge gestationnel au moment du diagnostic (RRA : 0,81 [IC à 95 % : de 0,70 à 0,93] par semaine; $p = 0,005$). En revanche, l'obtention d'un score z plus élevé pour la l'aorte ascendante (RRA : 0,65 [IC à 95 % : de 0,43 à 0,94] par z; $p = 0,029$) et une aorte transverse de plus grande dimension (RRA : 0,44 [IC à 95 % : de 0,18 à 0,97]; $p = 0,05$) s'accompagnaient d'une baisse du risque d'intervention.

Conclusions : Dans les cas de coarctation soupçonnée chez un fœtus, les variables associées à une intervention comprenaient une aorte ascendante et une aorte transverse de plus petite taille et un plus jeune âge gestationnel au moment du diagnostic auxquels s'ajoute la découverte d'une augmentation de la vitesse maximale du flux sanguin au niveau de l'aorte ascendante objectivée par écho-Doppler.

Methods

Study design and patient population

This was a single-centre retrospective cohort study. Patients with a prenatal diagnosis of a suspicion of aortic coarctation from January 2005 to December 2015 were identified from institutional fetal and cardiac surgical databases. This included patients referred for suspicion of coarctation in addition to patients referred for other reasons.

Patients were included if the suspicion of coarctation warranted postnatal observation that included repeated blood pressure monitoring to detect emerging arm-leg pressure gradients with ductal closure as well as a cardiac assessment with an echocardiogram before discharge. Cases deemed a low risk of neonatal coarctation were admitted to the neonatal intensive care unit at the adjacent tertiary care maternity hospital ("low likelihood") whereas those with an increased likelihood were transferred to the Hospital for Sick Children either with or without starting intravenous prostaglandin treatment ("high likelihood"). All patients were counselled by one of the 8 fetal cardiologists at our institution for either a high or low likelihood of needing intervention and this was communicated to the referring physician in the clinical note. All fetal cases after 2009 were then reviewed at a monthly perinatal meeting when the patients were reaching their third trimester. This meeting is attended by high risk obstetricians, fetal cardiologists, neonatologists, intensivists, and a ward cardiologist. At this meeting the risk stratification is reviewed, and a final perinatal plan determined by the group. If this is discordant from the first clinical note, an addendum is added to the clinical note and sent to the referring physician.

Patients who were initially referred for suspected coarctation but had a normal fetal echocardiogram were not included in this study. Patients who had a fetal echocardiogram reported as normal but were subsequently diagnosed and intervened upon with aortic coarctation postnatally were included and classified as a "missed diagnosis." Patients were included when the left ventricle was apex-forming and there was antegrade flow across the mitral and aortic valves.

Intervention was defined as primary coarctation repair, staged coarctation repair (hybrid operation), or catheter balloon dilation resulting in a biventricular (BV) circulation within 6 months of life.

Patients were excluded when there were associated cardiac lesions that would require postnatal surgical or catheter intervention within the time frame of the primary outcome. This included patients with moderate or severe aortic stenosis, moderate to large VSDs, double outlet right ventricle, transposition of the great arteries, interruption of the aortic arch, and atrioventricular septal defect. Fetuses with lethal chromosomal abnormalities diagnosed antenatally or postnatally, cases of intrauterine demise, and cases that underwent termination of pregnancy were excluded. Perioperative mortality was defined as death within 30 days of surgery or hospital discharge. Prostaglandin dependence, an arm-leg blood pressure gradient > 20 mm Hg, weak/absent femoral pulses, and decreased LV function are indications for surgical repair at our institution. The surgical strategy at our institution is repair using extended end-to-end anastomosis via a left thoracotomy when the transverse arch is deemed suitable in size. Complete arch reconstruction via sternotomy is performed in the presence of a severely hypoplastic transverse arch or otherwise complex arch anatomy. A hybrid surgery, consisting of bilateral pulmonary artery banding with stenting of the arterial duct, is performed in the setting of hypoplasia of the left ventricle where BV repair might be suitable at a later date. Patients with confirmed coarctation older that 3 months of age with preserved ventricular function and an arm-leg blood pressure gradient of > 20 mm Hg typically will typically undergo balloon dilation of the aorta. The study received approval from the institutional research ethics board.

Echocardiography assessment

Fetal echocardiograms were analyzed offline (Syngo Dynamics version V10; Siemens Medical Solutions, USA). The first diagnostic fetal echocardiogram performed at our institution was reviewed. Measurements of aortic valve annulus (5-chamber view), aortic:pulmonary valve ratio, mitral valve and tricuspid valve annulus (4-chamber view), mitral valve:-tricuspid valve ratio, ascending aorta (AAo), transverse aortic arch, and isthmus measurement (sagittal arch view), isthmus: duct ratio, RV end diastolic dimension (RVED), LV end diastolic dimension (LVED), RVED:LVED ratio, and LV and RV length were made according to published standards.[15] AAo pulsed wave Doppler was taken from the 3- or 5-chamber view in the proximal AAo. The AAo pulsed wave Doppler with the best alignment at the level of the AAo just above the aortic valve annulus was chosen. Doppler tracings requiring more than 30° of angle correction were not included in analysis. Peak AAo pulse wave Doppler was considered normal below 100 cm/s[16] and normal ductus arteriosus pulse wave Doppler below 180 cm/s.[17] Arterial duct and isthmal pulse wave Doppler traces were taken in the sagittal ductal arch view. Colour Doppler was used to record flow direction across the foramen ovale and transverse arch (sagittal or high three-vessel view). Flow in the transverse arch was noted as antegrade, bidirectional, or retrograde on the basis of colour and/or pulsed wave Doppler when available. Mitral and tricuspid inflow patterns were classified as monophasic or biphasic. Continuous flow in the transverse arch was noted as present or absent. Z scores, where appropriate, were used in conjunction with gestational age.[13,18] All fetal echocardiogram reports were reviewed and all necessary parameters were recorded. All fetal echocardiographic images were reviewed and any additional measurements were recorded by a single investigator (C.M.) who was blinded to clinical outcome. A third of the fetal echocardiograms were reviewed by a second investigator (L.E.N.) who was also blinded to outcome, and in cases of diagnostic uncertainty by the first investigator, the case was also reviewed by the second investigator.

All first diagnostic postnatal echocardiograms were reviewed by a single investigator (L.E.N.) blinded to clinical outcome, and relevant variables were extracted from the echocardiography report. Cardiovascular dimensions were converted to age- and body surface area-adjusted institutional z-score values with values between −2 and 2 z-scores from the normal mean considered as within the normal range. The presence of a bicuspid or unicuspid aortic valve, any mitral valve abnormalities, size of the left ventricle, and presence or absence of endocardial fibroelastosis were recorded. The diagnosis of aortic stenosis severity was on the basis of mean gradient (mm Hg) and graded as follows[19]: mild $<$ 20 mm Hg; moderate, 20-39 mm Hg; and severe $>$ 40 mm Hg. We compared prenatal and postnatal measurements of aortic, mitral, and tricuspid valve annulus sizes.

Statistical analysis

All variables were summarized and between group differences assessed using Wilcoxon sum rank tests, *t* tests, or Fisher exact tests. Binomial logistic regression was used to analyze the outcome variable, "no intervention" and "primary coarctation or staged coarctation repair." The least shrinkage and selection operator was used to select candidate risk factors with an optimal tuning parameter determined through tenfold cross-validation. Upon the selection of "important" risk factors (ie, risk factors associated with the outcome), the ordinary binomial logistic regression was used to quantify the association between the outcome variable and risk factors using odds ratios. The risk factor analysis (tenfold cross-validated least shrinkage and selection operator regression) was performed 100 times. Model fit was calculated using the model χ^2 statistics, which was also used to compare the various models with each other. The number of times a given risk factor was selected is reported as "reliability," where appropriate. The corresponding 95% confidence intervals (CIs) and *P* values were calculated using Wald statistics.

Results

Patient population

There were 134 patients included who were diagnosed with suspected aortic coarctation during the study period. This included 1 patient with a reported normal fetal echocardiogram who developed coarctation postnatally. We excluded 24 patients with additional major cardiac anomalies. One fetus with Turner syndrome and 2 fetuses with trisomy 13 confirmed using fetal karyotyping suffered in-utero demise and were excluded. This left 107 fetuses included for analysis (Fig. 1). Postnatal recommendations were made for 106 patients. Forty-four patients (42%) were considered "low likelihood" and 62 patients (58%) were considered "high likelihood" of developing clinically significant postnatal aortic arch obstruction. Median gestational age at first fetal echo was 32 weeks (interquartile range [IQR], 23-35 weeks; range, 18-41 weeks). In 45 cases (42%) the first fetal echocardiogram was performed in the second trimester, and in 62 (58%) the first fetal echocardiogram was in the third trimester. No fetal echocardiograms were performed in the first trimester.

Patients were predominately referred for suspected cardiac anomaly in 93% (n = 100) which included RV/LV size discrepancy, suspicion of coarctation, and suspicion of hypoplastic left heart syndrome. Other referral indications included screening because of the presence of extracardiac anomalies and for a family history of congenital heart disease. Mean maternal age at diagnosis was 30 ± 6 years. There were 5 mothers with gestational diabetes. Extracardiac abnormalities were identified in 18 patients (17%), which included genitourinary abnormalities in 9 patients, limb anomalies in 7 patients, and minor brain anomalies in 2 patients. Prenatal genetic testing was performed in 30 patients (27%) and abnormalities were identified in 10 of those tested, which included trisomy 21 in 3 patients, 1 of whom required intervention, Turner syndrome in 6 patients, 3 of whom required intervention, and Noonan syndrome in 1 patient who did not require intervention. Fertility aids (in vitro fertilization or in utero insemination) were used in 5 pregnancies. There were 4 twin pregnancies. There were no incidences of twin to twin transfusion syndrome.

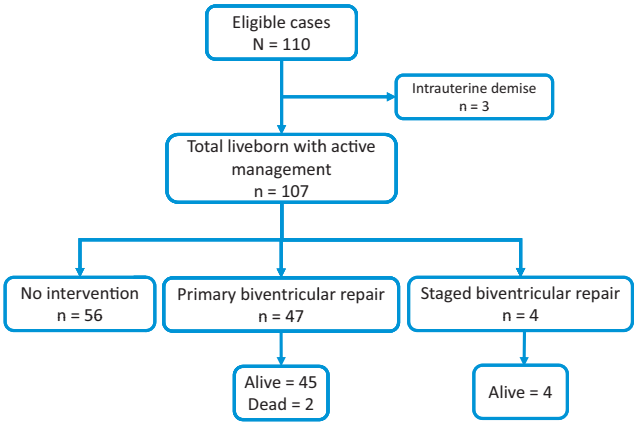

Figure 1. Outcome of eligible fetal cases.

Outcome of liveborn fetuses

Median gestational age at delivery was 39 weeks (IQR, 38-39 weeks) and mean birth weight 3.09 ± 0.71 kg. Preoperatively, 8% (n = 9) were intubated and 4% (n = 4) required inotropic support. Postnatal echocardiographic findings and associated cardiac lesions are outlined in Table 1. Coarctation of the aorta was confirmed postnatally in 48% (n = 51). Of those, 44 (86%) underwent an end to end anastomosis via a thoracotomy, 2 (4%) underwent a coarctation repair and transverse arch reconstruction through a sternotomy, 4 patients (8%) underwent a hybrid procedure and 1 patient (2%) underwent a balloon dilation of a coarctation. The remaining 52% (n = 56) after clinical and echocardiographic assessment did not develop coarctation at initial assessment/admission nor during subsequent follow-up. Of 62 patients in the high likelihood group, 46 patients (74%) developed coarctation that required intervention. Of 44 patients in the low likelihood group only 5 of them (11%) subsequently developed coarctation requiring intervention. The false positive rate (high likelihood patient who did not require intervention) was 16/106 (15%) and the false negative rate (low likelihood patient who did require intervention) was 5% (5/106).

No patient required VSD closure or aortic valve intervention at the time of coarctectomy or subsequently at follow-up. Presence of a small VSD, bicuspid aortic valve, posterior shelf, and left superior vena cava were significantly more common in the intervention group. Median age at intervention was 4 days (IQR, 3-6 days). Patients with a bicuspid or unicuspid aortic valve (n = 48) were more likely to undergo intervention than patients with a trileaflet aortic valve (n = 58; 79% vs 21%; $P < 0.001$). No patients were diagnosed postnatally with moderate to severe aortic stenosis or had developed stenosis at last follow-up. No patients were diagnosed with supravalvar aortic stenosis. Postnatally, all cases had morphologically normal mitral valves. The aortic valve z scores postnatally were smaller in the intervention group compared with the nonintervention group (−4.7 ± 2.2 vs −2.7 ± 1.7; $P < 0.001$). The mitral valve z scores similarly were smaller in the intervention group (−4.2 ± 1.7 vs −1.5 ± 1.6; $P < 0.001$).

Fetal echocardiographic findings

Fetal echocardiographic findings are outlined in Table 2. Patients with confirmed coarctation requiring intervention postnatally were diagnosed earlier, had higher AAo peak Doppler velocities, had smaller z scores of the aortic valve, mitral valve, AAo, LV end diastolic dimension and had a persistent left superior vena cava. Neither continuous flow at the aortic isthmus, nor the presence of a posterior shelf were associated with postnatal intervention. The pulmonary valve z score was greater in patients requiring postnatal intervention. Observed differences in isthmus:duct ratio, presence of posterior shelf, mitral:tricuspid valve ratio, continuous flow at isthmus, and presence of a small VSD were not statistically significant between the groups.

We diagnosed a bicuspid or unicuspid valve in 45% (n = 48) on postnatal echocardiography. Of patients with a bicuspid/unicuspid aortic valve who required intervention, their peak AAo Doppler velocity was higher than in patients with a normal trileaflet aortic valve (diagnosed postnatally) who required intervention (odds ratio, 4.92 [95% confidence interval (CI), 1.53-31.90] vs 1.76 [95% CI, 0.90-3.68]; $P = 0.032$).

There was no difference in isthmus pulse wave Doppler between the groups. In all cases the RVED measurements were within normal for gestational age with no difference between the 3 groups, whereas the LVED z scores were on the smaller end of normal or abnormal for body surface area. There was no difference observed between the groups in RV end diastolic dimension:LV end diastolic dimension ratio.

Factors associated with requiring a primary or staged BV repair

Univariable and multivariable risk factors for intervention are listed in Table 3. Increased peak AAo Doppler velocity and earlier gestational age were associated with increased risk for postnatal intervention in multivariable analysis. The predictive ability of the AAo Doppler velocity increased with each 20 cm/s velocity. Greater AAo z-score and greater transverse aorta diameter were associated with a decreased risk of postnatal intervention in multivariable analysis. Isthmus:duct ratio, mitral:tricuspid ratio, presence of a posterior shelf, continuous flow at isthmus, and anomalous transverse arch flow were not risk factors for postnatal intervention. Presence of a left superior vena cava was associated with increased odds of postnatal intervention in univariable analysis only.

For the multivariable predictive model, the area under the receiver operating characteristics (ROC) curve was 0.923 (95% CI, 0.87-0.97) with performance metrics as follows; accuracy was 0.86, sensitivity 0.89, specificity 0.82, positive predictive value 0.85, and negative predictive value 0.88. Excluding AAo Doppler velocity from the model significantly reduced model performance (area under the ROC curve, 0.877 [95% CI, 0.81-0.94]; accuracy, 0.80; sensitivity, 0.68; specificity, 0.94; positive predictive value, 0.93; and negative predictive value, 0.73). Table 4 shows the difference between the clinical prediction cited by the fetal cardiologist and the perinatal group and the multivariable model with and without the AAo velocity. The clinical prediction overall categorized

Table 1. Postnatal echo data

Variable	No intervention (n = 56)	BV repair (n = 47)	Staged BV repair (n = 4)	*P* value
Age at first echo, days	1 (0-1)	0 (0-1)	0 (0-1)	0.005
Mean weight at echo, kg	2.96 ± 0.80	3.22 ± 0.59	2.84 ± 0.47	0.142
Posterior shelf	2 (4)	34 (72)	3 (75)	< 0.001
Mean isthmus diameter, cm	0.40 ± 0.10	0.28 ± 0.08	0.34 ± 0.10	< 0.001
Mean transverse arch z-score	−2.7 ± 1.6	−4.9 ± 1.7	−5.5 ± 2.8	< 0.001
Abnormal abdominal aorta Doppler	1 (2)	14 (33)	1 (33)	< 0.001
VSD present	4 (7)	16 (34)	1 (25)	0.002
Aortic valve morphology				< 0.001
Normal (trileaflet)	46 (82)	12 (26)	0 (0)	
Bicuspid	10 (18)	34 (74)	3 (75)	
Unicuspid	0 (0)	0 (0)	1 (25)	
Mean aortic valve z-score	−2.7 ± 1.7	−4.5 ± 2.0	−6.9 ± 3.1	< 0.001
Aortic stenosis				0.045
None	56 (100)	42 (89)	4 (100)	
Mild (mean gradient < 20 mm Hg)	0 (0)	5 (11)	0 (0)	
Mean mitral valve z-score	−1.5 ± 1.6	−4.0 ± 1.7	−5.5 ± 2.0	< 0.001
Mitral valve stenosis				0.26
None	56 (100)	45 (96)	4 (100)	
Mild (mean gradient 5-10 mm Hg)	0 (0)	2 (4)	0 (0)	
Mean LVEDD z-score	−3.1 ± 1.9	−4.8 ± 2.4	−4.8 ± 2.1	0.092
PDA shunt direction				< 0.001
All left to right	19 (40)	2 (4)	0 (0)	
Right to left in systole	29 (60)	39 (85)	4 (100)	
Right to left in diastole	0 (0)	5 (11)	0 (0)	
Mean tricuspid valve z-score	−0.9 ± 1.7	−0.3 ± 1.8	2.6	0.166
Tricuspid valve regurgitation				0.42
None/mild	55 (98)	44 (94)	4 (100)	
Moderate	1 (2)	3 (6)	0 (0)	
Severe	0 (0)	0 (0)	0 (0)	
RVOT obstruction				1.00
None	56 (100)	47 (100)	4 (100)	
PFO/small ASD	50 (89)	40 (85)	3 (75)	0.42
PFO shunt direction				0.45
Left to right	49 (100)	37 (97)	2 (100)	
Right to left	0 (0)	0 (0)	0 (0)	
Bidirectional	0 (0)	1 (3)	0 (0)	
Mean RVEDD z-score	2.6 ± 1.9	3.0 ± 1.8	3.7 ± 0.3	0.62
Left SVC	3 (5)	5 (11)	2 (50)	0.028
LV function				0.106
Normal	55 (98)	45 (96)	3 (75)	
Mild	1 (2)	1 (2)	0 (0)	
Moderate-severe reduced	0 (0)	1 (2)	1 (25)	
Mean LVEF, %	71 ± 7	69 ± 14	71 ± 12	0.52
RV function				0.079
Normal	53 (95)	43 (91)	3 (75)	
Mild	3 (5)	4 (9)	0 (0)	
Moderate-severe reduced	0 (0)	0 (0)	1 (25)	

Continuous variables are summarized as median (interquartile range). Dichotomous and polychotomous variables are summarized as n (%) of patients.

ASD, atrial septal defect; BV, biventricular; echo, echocardiography; LV, left ventricle; LVEDD, left ventricular end diastolic dimension; LVEF, left ventricular ejection fraction; PDA, patent ductus arteriosus; PFO, patent foramen ovale; RV, right ventricle; RVEDD, right ventricular end diastolic dimension; RVOT, right ventricular outflow tract; SVC, superior vena cava; VSD, ventricular septal defect.

more patients in the "high likelihood" group, resulting in more false positive rates. In contrast, the multivariable model including the AAo velocity had a higher overall accuracy. The addition of the AAo velocity showed better balance of positive and negative predictions. The difference in the model fit expressed as the χ^2 statistics of the different models with and without AAo peak Doppler in addition to the other risk factors (earlier gestational age at echocardiography, transverse arch diameter, and AAo z-score) is depicted in Figure 2 and was statistically significant ($P < 0.001$).

Medium-term outcomes

Median follow-up for the entire cohort was 116 days (IQR, 7 days to 2.7 years). Follow-up for the patients who underwent intervention was 790 days (IQR, 44 days to 5.6 years). At last follow-up, there were 105 survivors (98%). Two patients who underwent BV repair died from noncardiac reasons which were: congenital lymphangiectasia in the setting of Turner syndrome (42 days postoperatively) and in a motor vehicle accident at 4 years old. All 4 patients who underwent a hybrid procedure were successfully converted to a BV circulation. Those 4 patients had an apex-forming left ventricle, however they all had mitral and aortic valve hypoplasia deemed too small to sustain a BV repair in the neonatal period. Only 1 patient at last follow-up had a resting arm-leg blood pressure gradient of > 20 mm Hg. No patient required reintervention for arch obstruction. No patient had echocardiographic evidence of pulmonary hypertension. All patients who underwent a staged BV repair

Table 2. Fetal echo variables

Variable	No intervention (n = 56)	BV repair (n = 47)	Staged BV repair (n = 4)	*P* value
Gestational age at first echo, weeks	35 (32-36)	24 (21-31)	27 (22-32)	< 0.001
Hydrops	1 (2)	0 (0)	0 (0)	1.00
EFE	0 (0)	0 (0)	0 (0)	1.00
LSVC	2 (4)	5 (11)	2 (50)	0.01
Mean AAo peak Doppler, cm/s	76 ± 22	89 ± 35	104 ± 46	0.052
Peak arterial duct Doppler, cm/s	95 (70-122)	70 (56-92)	116 (92-133)	0.004
Mean isthmus peak Doppler, cm/s	116 ± 37	106 ± 39	146 ± 9	0.30
Mean aortic valve annulus z score	−1.1 ± 1.2	−1.6 ± 1.8	−3.5 ± 0.8	0.007
Mean mitral valve z-score	−2.3 ± 1.3	−3.3 ± 1.5	−4.5 ± 1.6	0.001
Mitral valve inflow pattern				1.00
Biphasic	55 (98)	42 (98)	4 (100)	
Monophasic	1 (2)	1 (2)	0 (0)	
Mean tricuspid valve annulus z-score	−0.5 ± 1.2	−0.5 ± 1.1	−0.8 ± 0.4	0.77
Mean pulmonary valve z-score	0.8 ± 1.4	1.6 ± 1.5	1.4 ± 0.4	0.03
Pulmonary vein Doppler				0.03
Normal	50 (100)	41 (98)	4 (100)	
Abnormal	0 (0)	1 (2)	0 (0)	
MV:TV ratio	0.70 (0.63-0.79)	0.64 (0.58-0.73)	0.58 (0.51-0.67)	0.086
Mean ascending aorta z-score	−1.4 ± 1.5	−2.8 ± 1.5	−4 ± 2	< 0.001
Mean transverse arch diameter, cm	0.39 ± 0.12	0.24 ± 0.08	0.22 ± 0.09	< 0.001
Mean isthmus:duct ratio	0.58 ± 0.17	0.52 ± 0.25	0.44 ± 0.16	0.40
Mean RVEDD z-score	−0.1 ± 1.4	0.2 ± 1.0	0.6 ± 1.1	0.23
Mean LVEDD z-score	−2.8 ± 1.6	−2.7 ± 1.4	−4.8 ± 1.9	0.032
Mean RVEDD:LVEDD ratio	0.63 ± 0.15	0.62 ± 0.15	0.45 ± 0.14	0.129
Arch appearance				0.30
Normal	53 (95)	44 (94)	4 (100)	
Tortuous	3 (5)	3 (6)	0 (0)	
Continuous flow at isthmus	14 (25)	20 (43)	1 (25)	0.24
Posterior shelf	9 (16)	11 (23)	0 (0)	0.48
VSD	4 (7)	9 (20)	0 (0)	0.23
Arterial duct flow				1.00
Right to left	54 (100)	45 (100)	4 (100)	
Left to right	0 (0)	0 (0)	0 (0)	
Bidirectional	0 (0)	0 (0)	0 (0)	
Transverse arch flow				0.079
Antegrade	30 (54)	33 (70)	2 (50)	
Retrograde	7 (13)	9 (19)	0 (0)	
Bidirectional	18 (33)	5 (11)	2 (50)	
PFO shunt direction				0.047
Right to left	52 (93)	43 (91)	4 (100)	
Left to right	3 (5)	2 (4)	0 (0)	
Bidirectional	1 (2)	2 (4)	0 (0)	

Continuous variables are presented as median (interquartile range). Dichotomous and polychotomous variables are presented as n (%) of patients.

AAo, ascending aortic; BV, biventricular; echo, echocardiography; EFE, endocardial fibroelastosis; LSVC, left superior vena cava; MV, mitral valve; PFO, patent foramen ovale; RVEDD, right ventricular end diastolic dimension; TV, tricuspid valve; VSD, ventricular septal defect.

were alive at last follow-up. At last follow-up, no patient who was initially diagnosed as having a normal arch developed a subsequent coarctation.

Discussion

Prediction of outcome for suspected coarctation of the aorta remains a challenge. Despite the index of suspicion in our selected cohort, a neonatal intervention was only required in approximately 50%. This is in keeping with other series in which the incidence of true coarctation ranged between 30% and 65%, depending on the inclusion criteria.[14,20-22] Coarctation of the aorta cannot be reliably diagnosed prenatally by one single measurement or parameter, but instead suspicions are heightened when there are multiple parameters outside of the expected range. Some of these parameters have been highlighted in previous studies, including a smaller aortic valve and mitral valve z score, ventricular disproportion, and isthmal to duct ratio.[5,6,14,20,23] Those studies have focused on 2-dimensional measurements of the left-sided structures, and various ratios, but did not examine the role of Doppler in detail. The multivariable analysis identified that the addition of a peak AAo velocity improved the overall predictive power of the multivariable model (comprising gestational age at echo, transverse arch diameter, and AAo z score). The clinical physician's prediction was reasonably effective. However, clinicians tended to categorize the patients more frequently into the "high likelihood" category, creating a greater number of false positive rates. This makes sense, because the clinician would want to avoid unnecessary risk to the patient and the newborn, thereby admitting more patients to the ward or intensive care, and start prostaglandin treatment for a greater number of cases. This leads to an increase in hospital admissions, drives up the cost of health care, and can increase the stress to the family. The addition of the AAo velocity to the multivariable model allowed for improved positive and negative predictive value and overall accuracy, which has the potential to alter perinatal management.

Table 3. Results of the univariate and multivariate logistic regression for "BV or staged BV repair" compared with "no intervention"

Variable	Univariate OR (95% CI)	*P* value	Reliability, %	Multivariate OR (95% CI)	*P* value
LSVC	4.30 (0.98-29.82)	0.078	52	—	—
Postnatal chromosomal anomaly	0.44 (0.11-1.47)	0.20	65	—	—
Gestational age at birth, weeks	1.05 (0.84-1.32)	0.70	49	—	—
Gestational age at first echo, weeks	0.82 (0.75-0.88)	< 0.001	100	0.81 (0.70-0.93)	0.005
AAo peak Doppler (20 cm/s)	1.40 (1.05-1.91)	0.028	99	2.51 (1.54-4.58)	0.001
Peak PDA Doppler (20 cm/s)	0.75 (0.57-0.96)	0.033	27	—	—
Aortic valve z-score	0.72 (0.54-0.94)	0.018	24	—	—
Mitral valve z-score	0.58 (0.42-0.78)	0.001	57	—	—
Tricuspid valve z-score	0.97 (0.68-1.38)	0.87	39	—	—
Pulmonary:aortic valve ratio	6.17 (2.29-19.16)	0.001	37	—	—
Pulmonary valve z-score	1.61 (1.18-2.32)	0.005	77	—	—
MV:TV ratio	0.09 (0.00-0.86)	0.11	67	—	—
Ascending aorta z-score	0.53 (0.38-0.70)	< 0.001	96	0.65 (0.43-0.94)	0.029
Transverse arch diameter, mm	0.23 (0.12-0.38)	< 0.001	92	0.44 (0.18-0.97)	0.054
Isthmus diameter, mm	0.23 (0.11-0.42)	< 0.001	38	—	—
Arterial duct diameter, mm	0.64 (0.48-0.84)	0.002	19	—	—
Isthmus:duct ratio	0.20 (0.02-1.45)	0.14	36	—	—
RVEDD:LVEDD ratio	1.49 (0.63-3.64)	0.37	15	—	—
RVEDD z-score	1.26 (0.92-1.74)	0.16	62	—	—
LVEDD z-score	0.97 (0.75-1.24)	0.80	28	—	—
Continuous flow at isthmus	2.10 (0.93-4.86)	0.08	56	—	—
Posterior shelf	1.44 (0.54-3.90)	0.47	42	—	—
VSD	2.79 (0.84-10.87)	0.11	38	—	—
Anomalous transverse arch flow	0.57 (0.25-1.24)	0.16	19	—	—
PFO shunt direction			64	—	—
PFO shunt direction (left to right)	0.74 (0.09-4.63)	0.74		—	—
PFO shunt direction (bidirectional)	2.21 (0.21-48.52)	0.52		—	—

AAo, ascending aortic; BV, biventricular; CI, confidence interval; echo, echocardiography; LSVC, left superior vena cava; LVEDD, left ventricular end diastolic diameter; MV, mitral valve; OR, odds ratio; PDA, patent ductus arteriosus; PFO, patent foramen ovale; RVEDD, right ventricular end diastolic diameter; TV, tricuspid valve; VSD, ventricular septal defect.

The finding of an association between increasing peak AAo Doppler velocity and the development of true coarctation requiring intervention was an interesting discovery. No patient in our cohort had more than mild aortic stenosis, nor did any patient have supravalvar aortic stenosis, therefore, the higher Doppler velocity cannot be explained by discrete stenosis. Although some patients with coarctation had "normal" AAo Doppler velocities (ie < 100 cm/s), progressively higher AAo velocities should raise the suspicion of a neonatal intervention. One explanation could be that a smaller LV outflow tract in patients with true coarctation might result in a higher velocity. Postnatally, the velocities across the AAo were not increased. This might be explained by the changes in hemodynamics during the transition from the fetal to the postnatal circulation. Sheep models and more recently magnetic resonance imaging data, have shown that in patients with aortic coarctation, cardiac output is decreased by 20% coupled with decreased ascending aortic flow.[24-26] Despite the lower cardiac output, our cohort of coarctation still had an increased peak AAo velocity. Another possible explanation is that in patients with a bicuspid valve, which is dysplastic but not stenotic, a higher AAo velocity is seen. We showed that patients with a true coarctation and a bicuspid aortic valve (identified from postnatal imaging) had a higher AAo velocity prenatally than patients with a true coarctation and a morphological normal aortic valve. Because a bicuspid aortic valve cannot be reliably diagnosed prenatally, a higher AAo velocity might be a surrogate marker for the presence of a bicuspid valve.

Table 4. Comparison of clinical prediction and model accuracy

	PPV	Accuracy	NPV
Clinical prediction alone	74%	80%	89%
Model + AAo velocity	85%	86%	88%
Model − AAo velocity	93%	80%	73%

AAo, ascending aortic; NPV, negative predictive value; PPV, positive predictive value.

Other spectral and colour Doppler measurements were not useful. Mitral valve inflow and pulmonary vein Doppler patterns were unable to distinguish patients with true coarctation. Furthermore, mitral valve inflow patterns were normal despite a high number of patients with a hypoplastic mitral valve. Similarly, peak aortic isthmus velocity was not helpful in distinguishing patients with true coarctation, although this has been identified in a previous study of 62 cases.[20] We believe that capturing true isthmal velocity is challenging because distinguishing true isthmus from arterial duct is difficult.

A surprising finding was that neither continuous flow at the isthmus, nor bidirectional or retrograde flow in the transverse arch was seen more often in the true coarctation patients. Often the clinical assumption is that abnormal flow in the aortic arch is associated with greater degree of coarctation. However, continuous isthmus flow and retrograde or bidirectional flow was seen in a substantial number of patients who did not develop coarctation postnatally. In addition, colour interrogation of the arterial duct and foramen ovale showed normal right to left flow in almost all cases and therefore was unhelpful in diagnosing true coarctation.

Earlier gestational age at diagnosis was an important predictor of intervention. This likely represents the more severe end of the spectrum of fetal coarctation, compared

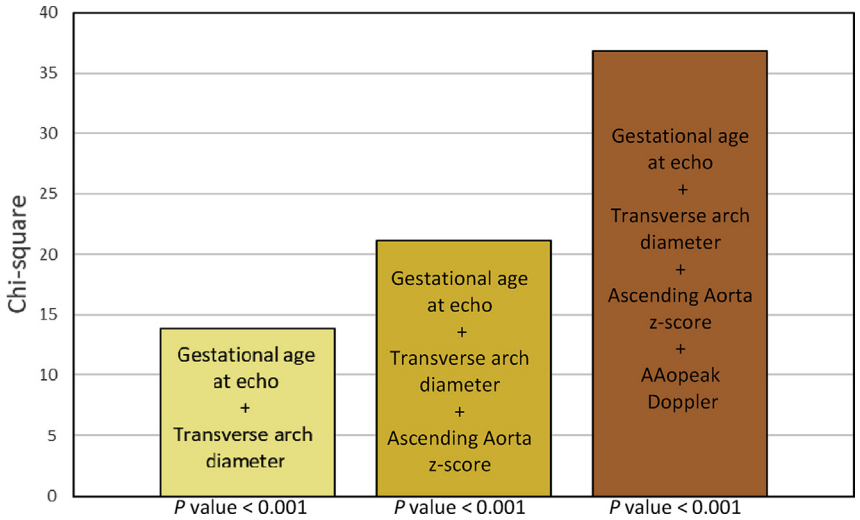

Figure 2. Difference between nested models as measured by Chi Square. The basic model includes only gestational age at echo. Incremental predictive value of transverse arch diameter, ascending aorta z-score and ascending aortic (AAo) peak Doppler.

with a later diagnosis in the third trimester. It is known that obstructive lesions can progress during gestation.[12,27-29] Our cohort had a significant number of cases referred in the third trimester (58%), which can be limited by poor echocardiography windows, fetal position, and the presence of a large tortuous arterial duct. However, when the cases are referred in midgestation, the cardiologist can be more confident that the outcome will likely be intervention. The reason for later gestation referral is most often that the initial anatomic scan performed at 18-20 weeks was normal, and a follow-up anatomic scan showed either an RV/LV size discrepancy or an abnormal 3-vessel view. Ventricular disproportion is most sensitive in the second trimester and has a high false positive rate of up to 80% by 34 weeks.[6,30]

One of the strengths of our study was the attempt to select the most homogeneous group of fetuses with suspected coarctation. Aortic coarctation is often associated with VSDs and aortic stenosis, which were excluded from the cohort. Despite our efforts to select cases with an adequate sized LV, 4 cases required a staged coarctation repair because of hypoplastic LVs that were unable to tolerate a neonatal BV repair.

Limitations

The retrospective nature of this study carries the usual limitations associated with this type of research, however all measurements were obtained by blinded investigators using a single digital system.

Doppler tracings of the mitral valve inflow, patent ductus arteriosus, and aortic isthmus were not available in all cases and are angle-dependent.[31,32] However, we had AAo peak Doppler in 93 of 106 cases. The peak velocity at the aortic isthmus was particularly difficult to ascertain. The gestational age at diagnosis was variable, with many cases presenting in the third trimester, and the number of false positive rates higher in the third trimester. We aimed to offset this limitation by using z scores for all valve and arch measurements.

We were unable to further investigate the association between the AAo velocity and an abnormal aortic valve because of inadequate patient numbers. This would be an important correlation to pursue in future studies.

Conclusions

In prenatally diagnosed cases of suspected coarctation of the aorta, the variables associated with postnatal intervention comprised of smaller AAo and transverse arch size, earlier gestational age at diagnosis, and a higher peak AAo Doppler velocity. The ideal next step would be to create a prospective multicentre registry of these cases to validate this model.

Disclosures

The authors have no conflicts of interest to disclose.

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