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Journal

Ultrasound in Obstetrics and Gynecology, 45(3)

ISSN

0960-7692

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Publication Date

2015-03-01

DOI

10.1002/uog.14667

Peer reviewed

HHS Public Access

Author manuscript

Ultrasound Obstet Gynecol. Author manuscript; available in PMC 2015 March 05.

Published in final edited form as:

Ultrasound Obstet Gynecol. 2015 March ; 45(3): 326–332. doi:10.1002/uog.14667.

Low Rate of Prenatal Diagnosis among Neonates with Critical Aortic Stenosis: Insight into the Natural History In Utero (Aortic Stenosis)

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Abstract

Objectives—To better understand the natural history and spectrum of fetal aortic stenosis (AS), we aimed to 1) determine the prenatal diagnosis rate of neonates with critical AS and a biventricular (BV) outcome; and 2) describe the findings at fetal echocardiography in prenatally diagnosed patients.

Methods—A multi-center, retrospective study was performed from 2000 to 2013. Neonates with critical AS who were discharged with a BV outcome were included. The prenatal diagnosis rate was compared to that reported for hypoplastic left heart syndrome (HLHS). Fetal echocardiographic findings in prenatally diagnosed patients were reviewed.

Results—Only 10 of 117 neonates (8.5%) with critical AS and a BV outcome were diagnosed prenatally, a rate significantly lower than that for HLHS in the contemporary era (82%; $p<0.0001$). Of the 10 patients diagnosed prenatally, all developed LV dysfunction by a median gestational age of 33 weeks (range, 28–35). When present, Doppler abnormalities such as retrograde flow in the aortic arch (n=2), monophasic mitral inflow (n=2), and left to right flow across the foramen ovale (n=8) developed late in gestation (median 33 weeks).

Conclusion—The prenatal diagnosis rate among neonates with critical AS and a BV outcome is very low, likely due to a relatively normal 4-chamber view in mid-gestation with development of significant obstruction in the 3rd trimester. This natural history contrasts with that of severe mid-gestation AS with evolving HLHS and suggests that the timing in gestation of significant AS has an important impact on subsequent left heart growth in utero.

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Disclosures: None

Keywords

Fetal cardiology; prenatal diagnosis; congenital heart disease; aortic stenosis; aortic valvuloplasty

Introduction

Congenital aortic stenosis (AS), which occurs in 0.2–0.5 per 1,000 live-births,[1–3] falls along the spectrum of congenital left heart obstruction and encompasses a range of clinical severity from an asymptomatic bicuspid valve in older children and adults to life-threatening, critical obstruction in newborns. Approximately 10% of patients present with neonatal critical AS[1] and require prostaglandin therapy and urgent intervention to maintain systemic perfusion. Subsequent management of these neonates may be challenging due to varying degrees of left heart hypoplasia, as well as coexisting mitral valve disease, ventricular dysfunction, and/or endocardial fibroelastosis. Careful assessment is required to determine whether a biventricular (BV) circulation or univentricular palliation, as performed for hypoplastic left heart syndrome (HLHS), should be pursued.[4–7] Despite the severity and complexity of neonatal critical AS and the benefit of prenatal diagnosis by facilitating delivery near a congenital heart center,[8–10] the prenatal diagnosis rate, particularly for those with a BV outcome, has not been reported.

In contrast, the prenatal diagnosis rate of HLHS, the most severe form of congenital left heart obstruction, has been well-described and is among the highest of all forms of congenital heart disease, ranging from 60 to 100%.[3, 11–18] The rate has steadily increased over time as prenatal ultrasound screening has become more widespread and fetal echocardiography has advanced.[3, 11] Whereas HLHS with mitral and aortic stenosis commonly manifests with severe AS and left ventricular (LV) dilation and dysfunction in mid-gestation,[19–22] prompting efforts at fetal aortic valvuloplasty,[22–24] we hypothesized that the prenatal diagnosis of neonates with critical AS and a BV outcome occurs infrequently due to a relatively normal-appearing heart at the time of routine mid-gestation ultrasound screening.

As part of a broader effort to better understand the natural history and spectrum of fetal AS, we aimed to determine the prenatal diagnosis rate of neonates with critical AS and a BV outcome across multiple centers and to place this rate in the context of prenatal detection of other congenital heart defects, particularly HLHS. Secondarily, among prenatally diagnosed patients, we sought to describe the fetal echocardiographic findings at presentation and throughout the remainder of gestation.

Methods

Patient Selection

For this multi-center, retrospective study, we included neonates with critical AS and a BV outcome who presented between January 1, 2000 and January 1, 2013. Neonates with critical AS were defined as those who required aortic valve intervention, either trans-catheter balloon dilation or surgical valvotomy, within the first 30 days of life. Patients who

underwent fetal intervention were not eligible for inclusion. Given the frequent association of AS and arch obstruction, neonates with critical AS and discrete coarctation were included. However, patients with more significant, multi-level left heart obstruction (i.e., Shone complex) with an abnormal mitral valve or supporting apparatus, subvalvar or supravalvar aortic obstruction, or diffuse arch hypoplasia were excluded. In addition, patients with ventricular septal defects or conoventricular abnormalities with posterior malalignment and arch interruption were excluded.

Since critical AS may be a heterogeneous disease from a morphologic standpoint with varying degrees of left heart hypoplasia, we included neonates with a common physiologic and clinical outcome: survival to discharge with a BV circulation. A BV circulation was defined as the LV supporting the full systemic cardiac output without any interval stage of univentricular palliation. In this manner, the study population differed not only from HLHS patients but also from "borderline" left heart patients who were managed as BV but died prior to discharge as a result of this strategy.

Participating Centers

Three congenital heart centers participated in this study: Boston Children's Hospital (Harvard Medical School); Benioff Children's Hospital (University of California-San Francisco School of Medicine); and Ann & Robert H. Lurie Children's Hospital of Chicago (Northwestern University Feinberg School of Medicine). Institutional Review Board approval was obtained from all participating centers with a waiver of consent.

Data Collection and Analysis

Patients were identified from hospital databases, and medical records and echocardiograms were reviewed at each center to ascertain the diagnosis of critical AS and a BV outcome. Eligible subjects were classified according to whether they received a prenatal or postnatal diagnosis. In the United States, routine prenatal care involves a screening ultrasound at 18–22 weeks gestation by an obstetrician or similar practitioner. Referral to a pediatric cardiologist for a fetal echocardiogram is performed if the mother and/or fetus are high-risk or if there is concern regarding the fetal heart on screening ultrasound. Only fetal echocardiograms among prenatally diagnosed patients were included for the present study. In the 3 cities in which our investigation was conducted (Boston, San Francisco, and Chicago), 96–98% of women receive prenatal care according to the National Center for Health Statistics.[25] We were unable to view the obstetric screening ultrasounds for the postnatally diagnosed patients; however, the vast majority received prenatal care, despite not being referred for fetal echocardiogram.

Among prenatally diagnosed patients, the following additional information was collected: maternal and fetal demographic characteristics, reason for referral for fetal echocardiogram, gestational age at diagnosis, and associated genetic and/or extracardiac diagnoses. De-identified clinical and echocardiographic data were sent to the lead site, Boston Children's Hospital, for further review and analysis.

Fetal and neonatal echocardiograms of prenatally diagnosed patients were reviewed by a single investigator (LF). Atrioventricular valves and ventricular dimensions were measured

at end-diastole, and semilunar valves were measured during systole per standard convention. Fetal and neonatal dimensions were normalized to gestational age- and body surface area-adjusted *z*-scores, respectively, using internal Boston Children's Hospital data. Ventricular size was also assessed qualitatively. Global systolic function was assessed qualitatively and quantitatively with the use of shortening fraction (SF).

Data regarding prenatal diagnosis rates are presented as frequency (percent), with 95% exact confidence intervals (CI) where appropriate. The one-sample test of proportions was used to compare the prenatal diagnosis rate of critical AS to the composite prenatal diagnosis rates of other forms of congenital heart disease from the literature: HLHS, other single ventricle lesions (including tricuspid atresia), tetralogy of Fallot, atrioventricular canal, and transposition of the great arteries. To obtain the composite prenatal diagnosis rate, the largest studies reporting the prenatal diagnosis rates of congenital heart disease in the contemporary era were examined (1995–2011); only those that reported absolute numbers of patients were included.[3, 11–18] For studies that reported different rates of prenatal diagnosis by era,[3, 11] the most recent era was used. The number of prenatally diagnosed patients across all studies was divided by the total number of patients with each defect to calculate the composite prenatal diagnosis rate. For the remaining statistical comparisons, the two-sample test of proportions was used.

Clinical and echocardiographic data are presented as median (range). Given the small number of prenatally diagnosed patients with serial studies available for review, the Wilcoxon signed-rank test was used to compare variables across gestation. Two-sided alpha levels of less than 0.05 were considered statistically significantly. Analysis was performed using Stata version 12.0 (StataCorp, College Station, TX).

Results

Prenatal Diagnosis of Neonatal Critical AS

Of 117 neonates with critical AS and a BV outcome, only 10 were diagnosed prenatally, yielding an overall prenatal diagnosis rate of 8.5% (CI: 3.4 – 13.7%). Three of the prenatally diagnosed patients and 13 of the postnatally diagnosed patients also had discrete coarctation; exclusion of these patients yielded no significant difference in the prenatal diagnosis rate (6.9% vs. 8.5%; p=0.66). Two of the prenatally diagnosed patients had a genetic diagnosis of Turner syndrome (45XO), and 1 had a 2-vessel umbilical cord. None had major extracardiac anomalies.

The prenatal diagnosis rates by center ranged from 5.3 to 9.2%, which were not significantly different. Figure 1 demonstrates the absolute number of prenatal and postnatal diagnoses by year. Comparing the prenatal diagnosis rates between the first and last 5 years of the study, 2000–2004 and 2008–2012, there was no statistically significant difference (3 out of 36 [7.7%] vs. 4 out of 43 [3.7 %]; p=0.32).

The prenatal diagnosis rate for neonatal critical AS was compared to the composite prenatal diagnosis rates for other forms of congenital heart disease from the contemporary literature (Table 1). Compared to HLHS, the prenatal diagnosis rate for critical AS was significantly

lower (p<0.0001). Moreover, compared to the prenatal diagnosis rate of transposition of the great arteries, considered one of the more difficult critical congenital heart defects to detect in utero,[3, 15, 18] the prenatal diagnosis rate of critical AS remained significantly lower (p<0.0001).

Clinical and Fetal Echocardiographic Features of Prenatally Diagnosed Patients

The gestational age at diagnosis and referral indication for fetal echocardiogram for the 10 prenatally diagnosed patients are listed in Table 2. The median gestational age at the time of diagnosis was 24.3 weeks (19.4 – 34.7). Of the 5 patients diagnosed in mid-gestation (19.4 – 22.6 weeks), 4 were referred for reasons other than suspected fetal cardiac disease. The fifth patient was referred for ventricular size discrepancy and was also diagnosed with coarctation postnatally. All 5 patients diagnosed later in gestation (26 – 34.7 weeks) had been receiving routine prenatal care earlier in pregnancy and were referred for suspected fetal cardiac disease and/or dysfunction.

Table 3 demonstrates the fetal echocardiographic findings at the time of diagnosis in mid-gestation versus late gestation and at the time of the last fetal study prior to birth. The 5 patients diagnosed in mid-gestation had trivial to mild flow acceleration across the aortic valve, which was noted to be thickened and/or dysplastic. However, LV function was preserved, and there was no significant LV hypoplasia or dilation. Doppler flow patterns, other than across the aortic valve, were normal with antegrade flow in the transverse aortic arch, biphasic mitral inflow, and right to left flow across the foramen ovale. As gestation progressed, LV dysfunction developed by a median gestational age of 34.6 weeks (28.4 – 35.3) in these patients. The evolution of in utero disease for a representative patient diagnosed in mid-gestation is depicted in Figure 2.

LV dysfunction, with a median SF of 17% (8 – 26%), developed among all prenatally diagnosed patients by a median gestational age of 33.2 weeks (28.1 – 35.3). In addition, other physiologic aberrations suggestive of significant left heart obstruction and/or elevated left-sided filling pressures were common in late gestation. Eight fetuses developed left to right flow across the foramen ovale by a median gestational age of 31.8 weeks (28.1 – 37), 2 were noted to have retrograde flow in the transverse aortic arch at 32.5 and 34.6 weeks, and 2 had monophasic mitral inflow at 34.6 and 36.5 weeks.

Figure 3 demonstrates the change in cardiac dimensions across gestation for 8 patients who had serial fetal echocardiograms available for review. The aortic valve was the smallest structure, with a median *z*-score of −1.7 (−4.3 – −1) at the time of diagnosis and −2.8 (−3.3 – −0.3) by the time of the last fetal study. Despite this downward trend, the difference was not statistically significant (p=0.12). The median mitral valve *z*-score was unchanged throughout the course of gestation (p=0.87). The LV demonstrated a modest trend toward dilation; however, no statistically significant difference was found (p=0.74).

Postnatal Course of Prenatally Diagnosed Patients

The median gestational age and weight at the time of birth were 37.5 weeks (34.0 – 39.1) and 3.1 kg (2.0 – 3.6), respectively. All patients were delivered at the tertiary-care center

where they were prenatally diagnosed and placed on prostaglandin therapy due to concern regarding critical obstruction and/or severe LV dysfunction. Prior to intervention, the median *z*-score for the aortic valve was −1.9 (−3.4 – −0.2). The median *z*-scores for the mitral valve and LV volume were normal at −0.2 (−0.7 – +2.7) and 0.04 (−2.6 – +2.9), respectively. Aortic valve intervention was performed at a median of 0 days of life (0 – 2). The median age at latest follow-up was 6.2 years (1 month – 11.8 years), and all patients were alive with a BV circulation.

Discussion

We found a very low prenatal diagnosis rate among neonates with critical AS and a BV outcome. The prenatal detection of this disease did not vary among centers, and notably, did not improve over the 13-year study period. Compared to the composite prenatal diagnosis rates of HLHS and other forms of congenital heart disease, the overall rate of prenatal diagnosis of neonates with critical AS was significantly lower. As opposed to forms of congenital heart disease that are underdiagnosed prenatally due to lack of routine incorporation of the outflow tract view, such as transposition of the great arteries,[14, 15, 17, 18, 26] we believe that the prenatal diagnosis rate for critical AS and a BV outcome is low due to a relatively normal 4-chamber view at the time of routine screening ultrasound, with development of significant pathology later in gestation.

In our small subset of prenatally diagnosed patients, we observed this natural history unfold. Four out of 5 fetuses diagnosed at mid-gestation were referred for echocardiogram for routine screening indications. Only subtle aortic valve pathology was noted at that time, with preserved LV function. By late gestation, the aortic valve disease progressed with development of LV dysfunction and other physiologic aberrations suggestive of hemodynamically significant obstruction. The other 5 prenatally diagnosed patients were detected only in late gestation, despite routine prenatal care earlier in pregnancy. These findings corroborate the study by Yagel *et al*, which demonstrated that despite detailed fetal echocardiograms performed in the 1st and/or 2nd trimesters among 22,050 pregnant women, AS accounted for nearly 20% of 3rd trimester diagnoses.[27]

In contrast to the findings in our current study, severe AS at mid-gestation, which progresses to HLHS with mitral and aortic stenosis by the time of birth, is frequently associated with significant LV dilation and/or dysfunction at the time of routine ultrasound surveillance[19–22] In other cases of prenatally diagnosed HLHS involving aortic and/or mitral atresia, the LV is often already hypoplastic at mid-gestation.[28] Either LV dilation or hypoplasia on the 4-chamber view at mid-gestation would prompt referral for fetal echocardiography by obstetric providers, explaining the high prenatal diagnosis rate for HLHS as compared to neonates born with critical AS.

While the natural history of severe mid-gestation AS that evolves to HLHS has been well-described and has led to efforts at fetal aortic valvuloplasty,[19–24,28] we report a distinct natural history; namely, that of severe late gestation AS that progresses to critical AS with a BV outcome by the time of birth. In our series of prenatally diagnosed patients, left-sided dimensions did not change significantly over the course of gestation, thus resulting in an LV

that was capable of supporting the systemic circulation after birth. While animal and stem-cell models have postulated that fetuses with HLHS experience irreversible myocardial damage in response to LV pressure overload and hypoxia, with altered stress-strain properties, myofibrillar disorganization, and persistence of fetal gene expression patterns,[29–32] we speculate that when significant AS develops later in gestation, the more mature myocardium responds differently. As such, significant left-sided growth arrest, as seen in patients born with HLHS,[26,33] does not occur. Aortic valve intervention in the neonatal period alone is sufficient to enable a BV circulation.

Recognition of the low prenatal diagnosis rate of neonatal critical AS, along with a better understanding of the natural history in utero, may enhance prenatal detection and perinatal outcome.[8–10] As standards for obstetric ultrasound are changing with incorporation of the outflow tract views,[34] more subtle findings may be detected at mid-gestation to prompt follow-up evaluation in the 3rd trimester. The addition of color Doppler at mid-gestation would likely augment the detection of mild aortic valve pathology; however, as detailed previously, the findings may remain subtle due to lack of significant disease. High-risk fetuses for the development of left ventricular outflow tract obstruction, such as those with a family history or Turner syndrome, may warrant subsequent evaluation regardless of mid-gestation findings. However, routine 3rd trimester ultrasound screening in a low-risk population, without the use of color Doppler, did not increase detection of congenital anomalies or alter perinatal outcome in a recent randomized, controlled trial.[35] Perhaps the most important implication of the current study is to help inform who may *not* benefit substantially from fetal aortic valvuloplasty, particularly in the 3rd trimester, as postnatal intervention alone may permit a BV outcome.

This study was limited by its cross-sectional, retrospective design. We were unable to review the mid-gestation screening ultrasounds from the referring providers for assessment of the 4-chamber view and whether the outflow tract view was incorporated. We inferred that the screening cardiac views were “normal” since patients were not referred for fetal echocardiogram. By defining cases based on postnatal diagnosis, we were unable to account for termination or fetal demises in the prenatal diagnosis rate. Finally, although we collaborated among high-volume fetal referral centers, there were relatively few fetal echocardiograms for analysis due to the low prenatal diagnosis rate. The lack of significant changes in cardiac dimensions across gestation for our series may, therefore, be due to the small sample size.

In conclusion, we believe that the very low prenatal diagnosis rate of neonates with critical AS and a BV outcome is predominantly due to lack of significant pathology at the time of routine ultrasound surveillance, which contrasts with the natural history of severe mid-gestation AS with evolving HLHS. The timing in gestation of hemodynamically significant obstruction, with differing stages of myocardial maturation and distinct genetic and environmental influences, presumably impacts subsequent left heart growth in utero. As summarized schematically in Figure 4, severe obstruction earlier in gestation tends to lead to more severe disease as myocardial damage ensues, resulting in an LV incapable of supporting the circulation, i.e., HLHS. On the other hand, obstruction later in gestation, as seen in the prenatally diagnosed cohort in our study, tends to produce less severe disease and

a potential BV outcome, i.e., critical AS. Since overlap of pathogenic processes may exist in the developing fetus, serial echocardiography is essential to monitor disease progression and to further enhance our understanding of the spectrum of fetal AS.

Acknowledgments

Sources of Funding:

This work was supported in part by the National Institutes of Health under award number: T32HL007572. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

This work was supported by the Kenrose Kitchen Foundation.

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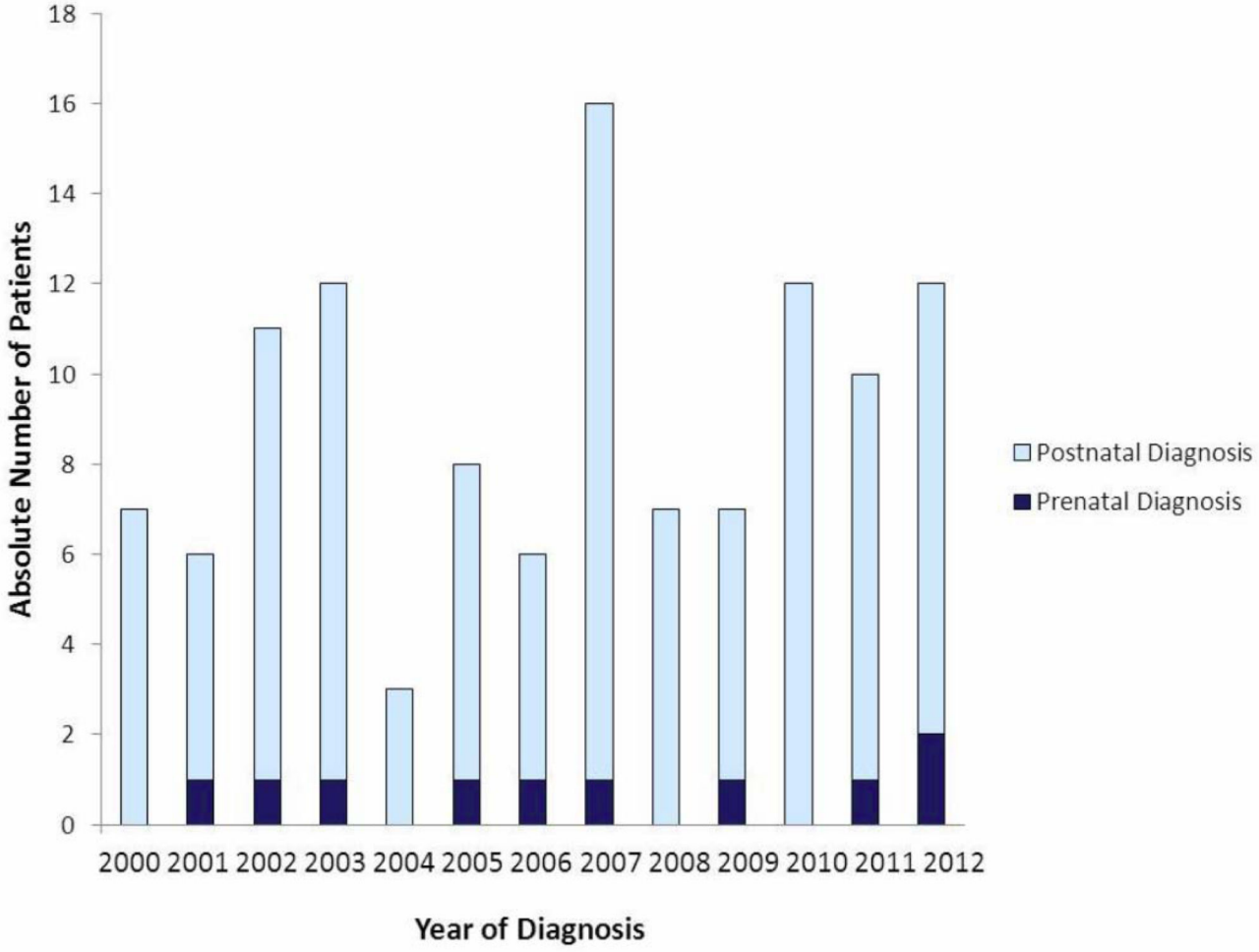

Figure 1.
Pre- and postnatal diagnosis of neonatal critical aortic stenosis with a biventricular outcome by year.

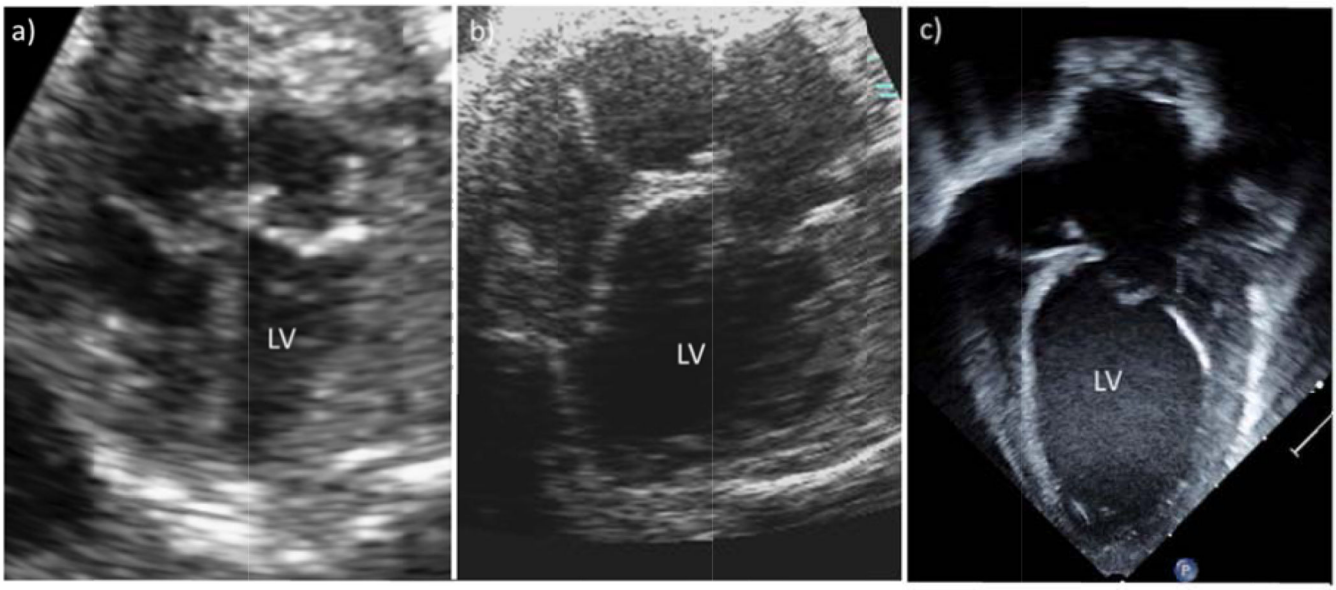

Figure 2.

Images of a prenatally diagnosed patient with neonatal critical aortic stenosis and a biventricular outcome referred for routine screening fetal echocardiogram at mid-gestation for family history of congenital heart disease: 1) 4-chamber view without obvious abnormality at approximately 22 weeks gestation; and b) abnormal 4-chamber view with LV dilation (and dysfunction, not shown) suggestive of hemodynamically significant obstruction at approximately 34 weeks gestation. The final image, c), demonstrates the postnatal findings of significant LV dilation prior to neonatal aortic valvuloplasty. (LV-left ventricle)

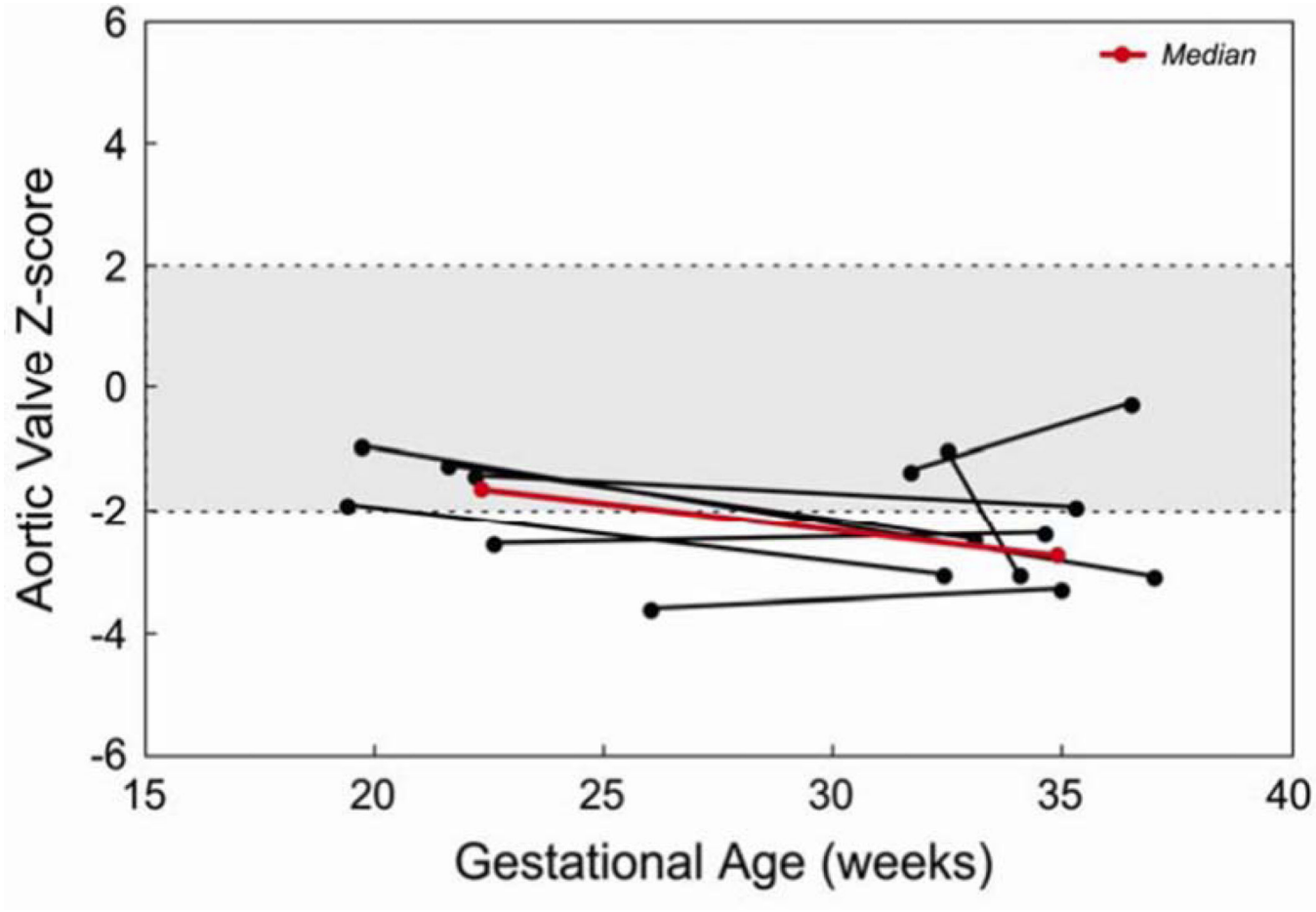

Figure 3.

Changes in cardiac dimension z-scores across gestation for patients prenatally diagnosed with critical aortic stenosis and a biventricular outcome: a) aortic valve; b) mitral valve; and c) left ventricular (LV) long-axis dimension. Eight out of 10 patients had serial fetal echocardiograms available for review. The shaded portions represent the normal range.

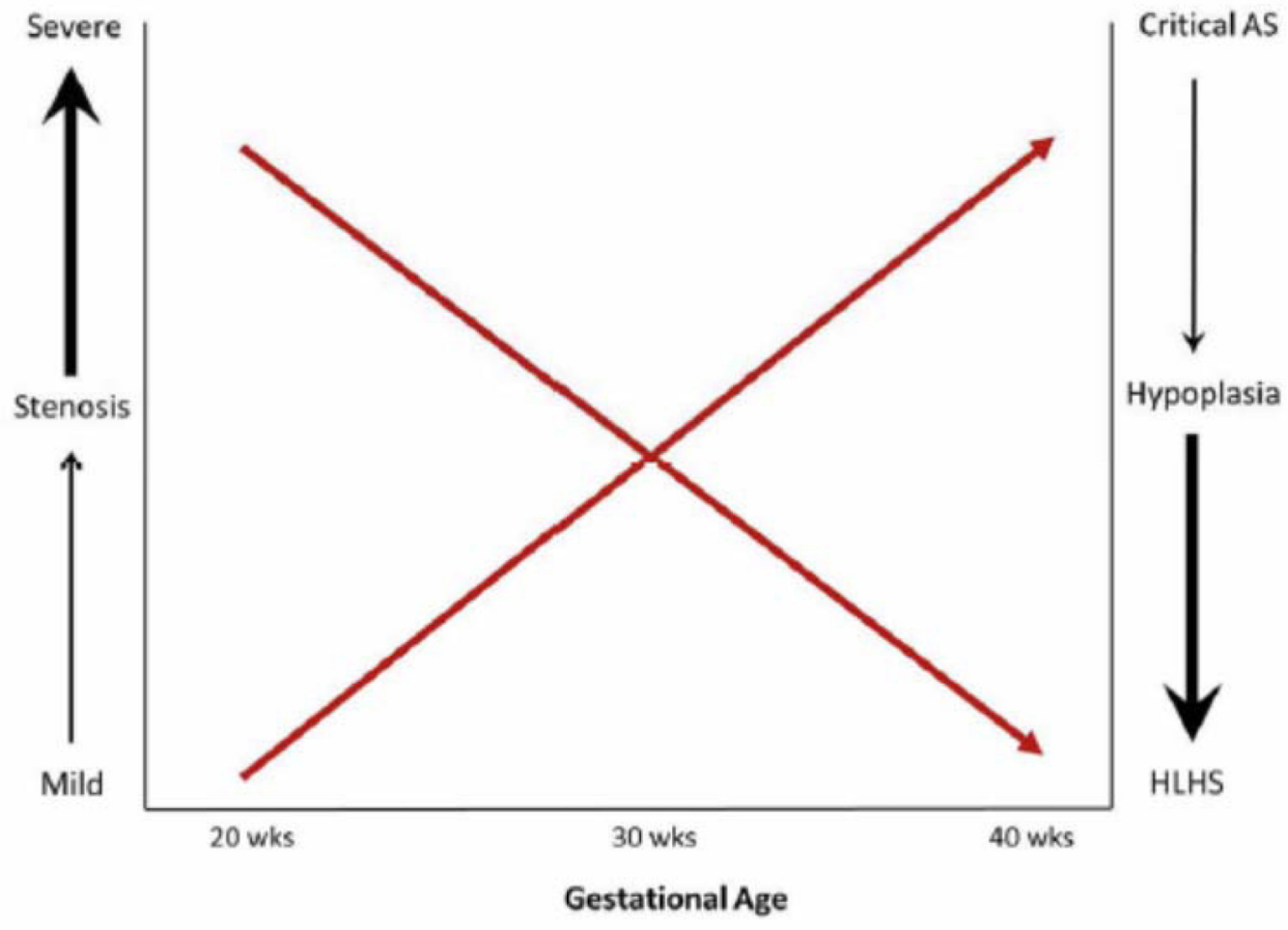

Figure 4.

Schematic diagram demonstrating the timing in gestation of aortic stenosis and its impact on the degree of left heart hypoplasia at birth (AS=aortic stenosis, HLHS=hypoplastic left heart syndrome).

Table 1

The prenatal diagnosis rate for neonatal critical aortic stenosis with a biventricular outcome compared to the published prenatal diagnosis rates for other forms of congenital heart disease in the current era (1995–2011).

Congenital Heart Disease	Range of Prenatal Diagnosis Rates	Composite Prenatal Diagnosis Rate (Absolute Numbers)	P-value Compared to Critical AS
HLHS[3, 11–18]	60–100%	82% (383/465)	p<0.0001*
Other single ventricle lesions[3, 14, 15, 17, 18]	50–100%	70% (105/149)	p<0.0001
Atrioventricular canal[3, 12–15, 17, 18]	24–83%	64% (225/349)	p<0.0001
Tetralogy of Fallot[3, 11–15, 17]	25–70%	40% (163/404)	p<0.0001
Transposition of the great arteries[3, 11–15, 17, 18]	15–72%	31% (131/427)	P<0.0001

Percentages were rounded.

* P-values were determined using the composite prenatal diagnosis rate from the published literature. Comparison of the absolute numbers of patients with each defect to critical AS yielded the same p-value.

AS=aortic stenosis, HLHS=hypoplastic left heart syndrome.

Table 2

Gestational age at time of diagnosis and referral indication for fetal echocardiogram for the 10 prenatally diagnosed patients.

Gestational Age at Diagnosis (weeks)	Referral Indication for Fetal Echocardiogram
19 3/7	Suspected fetal cardiac disease (ventricular size discrepancy with additional postnatal diagnosis of coarctation)
19 5/7	Family history of congenital heart disease, increased nuchal translucency
22	Family history of congenital heart disease
22 1/7	Genetic diagnosis (Turner syndrome)
22 4/7	Genetic diagnosis (Turner syndrome)
26	Suspected fetal cardiac disease
31 5/7	Suspected fetal cardiac disease
33 1/7	Suspected fetal cardiac disease
34	Suspected fetal cardiac disease, 2-vessel umbilical cord
34 5/7	Suspected fetal cardiac disease

Table 3

Fetal echocardiographic findings at diagnosis in mid-gestation (n=5) and late gestation (n=5) and at the time of the last fetal study (n=10) for patients prenatally diagnosed with neonatal critical aortic stenosis.

	Diagnosis		**Last Fetal Study**
	Mid-gestation 21.6 weeks (19.4 – 22.6)	***Late gestation 32.5 weeks (26.0 – 34.7)***	***All patients 34.6 weeks (32.4 – 37.0)***
Antegrade flow across AV	100% (5/5)	100% (5/5)	100% (10/10)
Peak velocity across AV	1.0–1.4 m/s	2.4–3.7 m/s	1.8–4.0 m/s
LV dilation	0% (0/5)	60% (3/5)	50% (5/10)
LV dysfunction	0% (0/5)	100% (5/5)	100% (10/10)
Presence of EFE	0% (0/5)	60% (3/5)	40% (4/10)
Mitral regurgitation	0% (0/5)	80% (4/5)	50% (5/10)
Retrograde flow in transverse aortic arch	0% (0/5)	20% (1/5)	20% (2/10)
Monophasic mitral inflow	0% (0/5)	20% (1/5)	30% (3/10)
Left to right flow across foramen Ovale	0% (0/5)	100% (5/5)	80% (8/10)
Flow reversal in pulmonary veins	0% (0/5)	0% (0/5)	10% (1/10)

Gestational ages and LV dimensions are presented as median (range). Echocardiographic findings are presented as frequency (percent).

AV=aortic valve, LV=left ventricle, EFE=endocardial fibroelastosis.