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Tricuspid Valve Disease With Significant Tricuspid Insufficiency in the Fetus: Diagnosis and Outcome

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The echocardiographic studies and clinical course of 27 fetuses (mean gestational age 26.9 weeks) diagnosed in utero with tricuspid valve disease and significant tricuspid regurgitation were reviewed. The diagnosis of Ebstein's anomaly was made in 17 of the fetuses, 7 had tricuspid valve dysplasia with poorly developed but normally attached leaflets and 2 had an unguarded tricuspid valve orifice with little or no identifiable tricuspid tissue. One fetus was excluded from data analysis because a more complex heart lesion was documented at autopsy. All fetuses had massive right atrial dilation and most who were serially studied had progressive right-sided cardiomegaly. Hydrops fetalis was found in six cases and atrial flutter in five.

Associated cardiac lesions included pulmonary stenosis in five cases and pulmonary atresia in six. Four fetuses with normal forward pulmonary artery flow at the initial examination were found at subsequent study to have retrograde pulmonary artery and ductal flow in association with the development of pulmonary stenosis (n = 1) and pulmonary atresia (n = 3). On review of the clinical course of the 23 fetuses (excluding 3 with elective abortion), 48% of the fetuses died in utero and 35% who were liveborn died despite vigorous medical and, when necessary, surgical management, many of whom had severe congestive heart failure. Of the four infants who survived the neonatal period, three had a benign neonatal course, all of whom were diagnosed with mild to moderate Ebstein's anomaly; only one had pulmonary outflow obstruction. An additional finding at autopsy was significant lung hypoplasia documented in 10 of 19 autopsy reports.

Tricuspid valve anomalies with tricuspid insufficiency can be identified echocardiographically in the fetus and should be searched for in the presence of right atrial enlargement. The prognosis for the fetus diagnosed in utero with significant tricuspid valve disease is extremely poor, with a prenatal course that includes progressive right heart dilation, with cardiac failure and lung hypoplasia in many and development of pulmonary stenosis or pulmonary atresia later in gestation in some.

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Congenital tricuspid valve disease associated with tricuspid regurgitation, including both Ebstein's anomaly and so-called tricuspid valve dysplasia, is usually well tolerated in older infants, children and adolescents (1–4). The majority of patients have minimal or no disability and many live well into adulthood (3). Although there is a greater incidence of death among affected infants who present in the newborn period with cardiomegaly, cyanosis and congestive heart failure (2,5–9), many survive with marked clinical improvement as their pulmonary vascular resistance decreases (3,4,9). In neonates with milder tricuspid valve disease, there may even be complete or near complete resolution of symptoms, as previously reported (3,4,10).

The diagnosis of any type of congenital heart disease in utero has been associated with poor outcome, possibly because a more severe spectrum of disorders is identified and there appears to be a higher incidence of associated malformations and chromosomal anomalies in this prenatally "presenting" group of patients (11–14). Preliminary studies (11,15) directed toward the prenatal diagnosis of congenital heart disease and a number of case reports (16,17) suggest a substantially worse prognosis for the fetus diagnosed with tricuspid valve disease, particularly when associated with significant tricuspid insufficiency. To date, however, no large study with a high percent of anatomically verified patients has focused specifically on the diagnosis and follow-up evaluation of prenatally detected tricuspid valve disease. Therefore, in the present study, we retrospectively studied the combined experience of three large fetal echocardiography referral centers with tricuspid valve disease and tricuspid regurgitation to document the forms of tricuspid disease encountered in utero and the subsequent outcome of these fetuses, with elucidation of associated findings that could be of prognostic importance.

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Table 1. Tricuspid Valve Disease in the Fetus (26 cases)

Case No.	Initial EGA (wk)	TVD	Add Cardiac Anomaly	Other Findings	Lung Hypoplasia	Course
1	19	UG	—	Hydrops, A flutter	–	IUFD (21 wk)
2	25	TD	—	Hydrops, ascites	–	IUFD (25 wk)
3	28	TD	—	Hydrops, A flutter	+	ND (12 h)
4	28	EA	—	—	–	IUFD (29 wk)
5	31	EA	—	Hydrops	+	IUFD (32 wk)
6	29	EA	—	—	+	IUFD (31 wk)
7	31	EA	VSD	Trisomy 13	Suspected	ND (1 day)
8	29	EA	PS	—		Survivor s/p valvuloplasty
9	19	EA	—	—	+	Elective abortion
10	37	EA	—	—	+	ND (10 days)
11	29	EA	—	Hydrops, A flutter	NA	IUFD (32 wk)
12	21	EA	—	—		Survivor
13	26	TD	—	A flutter	–	IUFD (29 wk)
14	29	TD	PAtr	—	NA	Death at 4 mos
15	19	EA	—	—	–	Elective abortion
16	28	EA	—	Hydrops, A flutter	+	IUFD (30 wk)
17	25	EA	—	—	–	Elective abortion
18	28	UG	PAtr	—	+	IUFD (29 wk)
19	32	EA	—	—	–	IUFD (35 wk)
20	28	EA	PAtr	—	+	ND (2 days)
21	27	TD	PS	—	+	ND (12 h)
22	20	TD	PS	—	–	NA (2 days)
23	27	TD	PAtr	—	+	IUFD (28 wk)
24	27	EA	PS	—	–	NA (4 days)
25	34	EA	—	—		Survivor
26	35	EA	PAtr	—	Suspected	ND (2 days)

Add = additional; A flutter = atrial flutter; EA = Ebstein's anomaly; EGA = estimated gestational age; IUFD = in utero fetal demise; NA = no autopsy; ND = neonatal demise; PAtr = pulmonary atresia; PS = pulmonary stenosis; TD = tricuspid dysplasia; TVD = tricuspid valve disease; UG = unguarded tricuspid valve orifice; VSD = ventricular septal defect; + = yes; – = no.

Methods

Study cases. We reviewed the history and echocardiographic studies of 27 fetuses with tricuspid valve disease and significant tricuspid regurgitation successfully diagnosed in utero at the Yale-New Haven Hospital, the University of Arizona Medical Center and the University of California–San Diego Medical Center. Referral to one of the three centers for fetal echocardiographic study was initiated primarily because of abnormal findings on a routine obstetric sonogram that included an abnormal atrioventricular valve (Fig. 1) or an asymmetric four chamber view (predominantly right atrial enlargement). This was the case for 17 of the 27 fetuses studied. Other reasons for referral included the presence of nonimmune hydrops fetalis in three, maternal lithium ingestion in three, a family history of congenital heart disease in two, a positive rubella titer in one and in utero tachycardia in one. No fetus had known in utero exposure to indomethacin or similar prostaglandin inhibitors.

Echocardiographic study. All fetuses had been evaluated using third generation, high resolution linear array or electronic sector scanners with Doppler capabilities. Fetal echocardiographic imaging of the two-dimensional cardiac anatomy and pulsed or continuous wave Doppler interrogation were performed using techniques that have been previously described (18–20). Imaging was performed with a 3.5 or 5 MHz transducer; a 3.5 MHz transducer had been used for the majority of Doppler studies. Doppler echocardiographic and color flow mapping studies were performed on either an Acuson, Toshiba or Hewlett Packard instrument. The severity of tricuspid valve regurgitation was judged on the basis of spatial extension of the regurgitant signal by color flow or spectral Doppler mapping and its relation to right atrial size.

Results

Clinical characteristics, associated lesions and outcome (Table 1). The estimated gestational age of the 27 fetuses at the time of the initial examination, based on standard sonographic measurements of biparietal diameter and abdominal circumference or femur length, or both, ranged from 19 to 35 weeks. One of the cases involved a twin gestation with one of the fetuses affected. Only one fetus was known to have a chromosomal abnormality (trisomy 13). No other fetus had any documented noncardiac defect. Autopsy confirmation of the diagnosis was available for 19 of the fetuses whose course resulted in in utero demise or death in the neonatal period.

One of the 27 fetuses was subsequently documented to

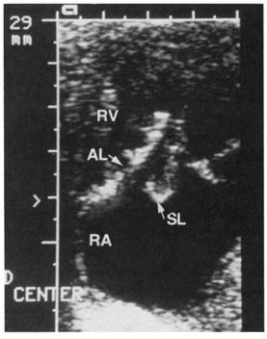

Figure 1. Case 22. Two-dimensional echocardiogram of tricuspid dysplasia initially diagnosed in a fetus at 20 weeks of gestation. The dysplastic-appearing tricuspid septal leaflet (SL) prolapses behind the thickened, redundant anterior leaflet (AL). RA = right atrium; RV = right ventricle.

have a more complex heart lesion than suggested by the initial prenatal echocardiogram and was excluded from consideration as it relates to the natural history aspect of this series of cases. Of interest, this fetus had a very rare form of L-transposition with left-sided Uhl's anomaly of the right ventricle, severe Ebstein's anomaly of the tricuspid valve and aortic atresia established at autopsy (infant died at 5 days of age). To our knowledge, such a combination of cardiac anomalies has not been previously described.

Types of tricuspid valve disease. On review of the 26 cases, three types of tricuspid valve anomalies were identified, all of which were associated with significant tricuspid regurgitation as demonstrated using spectral Doppler and color flow imaging in the presence of marked right atrial enlargement. The presence of significant tricuspid regurgitation was suspected if at least two of the following criteria were present: 1) marked right atrial enlargement, 2) half of the right atrial area filled with the tricuspid regurgitant jet on color flow imaging, or 3) the pulsed Doppler signal of tricuspid regurgitation was detectable at least halfway back to the right atrial wall from the tricuspid valve.

Ebstein's malformation. Seventeen fetuses were diagnosed with Ebstein's malformation of the tricuspid valve, with displacement of the leaflets (septal and posterior) into the right ventricular sinus and atrialization of the proximal right ventricular chamber. This was confirmed at autopsy in 11 cases and at cardiac catheterization, surgery or postnatal echocardiographic examination in four. By color flow imaging, the tricuspid regurgitant jet in fetuses with Ebstein's anomaly appears to originate at a level midway into the right ventricle (Fig. 2).

Tricuspid valve dysplasia. Seven of the 26 fetuses were diagnosed with tricuspid valve dysplasia, having normal insertion of all three leaflets at the tricuspid valve anulus. Morphologically, the leaflets appeared thickened and were frequently redundant or hypoplastic, with abnormal tethering of the anterior tricuspid leaflet to the right ventricular free wall. Six of the seven fetuses diagnosed with tricuspid valve dysplasia had autopsy confirmation of the abnormally structured valve. In one fetus (Case 2), all three leaflets were hypoplastic and nonfunctional, verging toward an essentially unguarded tricuspid valve orifice. In another fetus (Case 3), there were thickened tricuspid leaflets associated with idiopathic hypertrophic cardiomyopathy and notable right side involvement.

Figure 1 is a conventional two-dimensional echocardiographic image obtained in one fetus (Case 22) with tricuspid valve dysplasia and shows a very thickened, elongated anterior leaflet in addition to a dysplastic-appearing septal leaflet that prolapses behind the thickened leaflet. At autopsy, the tricuspid valve leaflets in this fetus were floppy and redundant and had a "mucoid" appearance. In fetuses with tricuspid valve dysplasia, two-dimensional color flow imaging demonstrated a tricuspid regurgitant jet that originated at the level of the tricuspid valve anulus.

Unguarded tricuspid valve orifice (Fig. 3). The diagnosis of unguarded tricuspid valve orifice, using the initial definition of Kanjuh et al. (21), was made in two fetuses. At ultrasound examination, there was no identifiable tricuspid leaflet tissue visualized at the tricuspid valve anulus along the ventricular septum or posterior free wall. At autopsy in both fetuses, only rudimentary leaflets were identified deep within the right ventricular chamber, which were not significantly mobilized from the ventricular wall.

Associated cardiac findings at echocardiography. All 26 fetuses had marked right atrial dilation. In several serially studied fetuses, there was progressive right-sided cardiomegaly, including three fetuses who had normal right ventricular size when initially studied. Right to left ventricular diameter ratio measured in seven cases from University of California–San Diego Medical Center ranged from 1.4 to 3.8, with a mean of 2.1 (normal ratio = 1.15).

In addition to right-sided cardiomegaly, other findings in the fetuses on initial examination included hydrops fetalis in six, with significant body edema, pleural effusions and ascites in one and atrial flutter in five (Cases 1, 3, 11, 13 and 16). Documentation of atrial flutter in all five was by two-dimensional M-mode imaging, as previously described by Kleinman et al. (22).

In seven fetuses, there were additional cardiac lesions discovered at the initial echocardiographic examination. These included pulmonary atresia in two and pulmonary stenosis in four. In the fetus with trisomy-13 (Case 7), a malaligned ventricular septal defect was associated with Ebstein's anomaly.

Development of pulmonary obstruction. At the initial examination performed in the second trimester, four fetuses

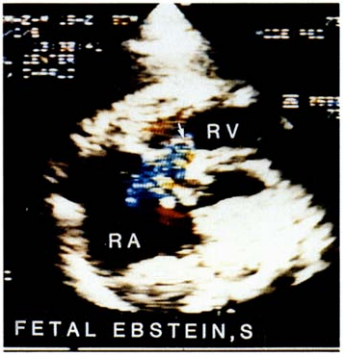

Figure 2. Case 20. Doppler flow echocardiogram obtained in a 32 week old fetus with Ebstein's anomaly of the tricuspid valve. The tricuspid septal leaflet is inferiorly displaced along the interventricular septum, with the tricuspid regurgitant jet (arrow) originating at a level midway into the right ventricle (RV). Abbreviations as in Figure 1.

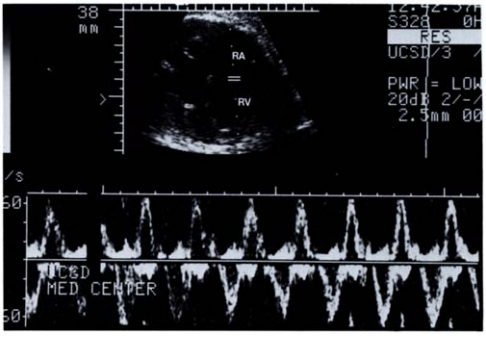

Figure 3. Case 18. Two-dimensional echocardiogram and pulsed Doppler recording obtained in a 28 week old fetus with an unguarded tricuspid valve orifice, showing low velocity bidirectional flow between the right atrium (RA) and right ventricle (RV). By pulsed Doppler ultrasound (below), systolic and diastolic flow velocities across the markedly dilated tricuspid valve anulus are essentially identical and no tricuspid leaflet tissue is visible in the two-dimensional image (above).

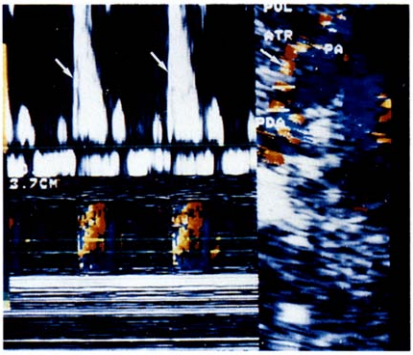

Figure 4. Doppler color flow echocardiogram in a 28 week old fetus with progressive development of pulmonary outflow obstruction that eventually progressed to pulmonary valve atresia (PVL ATR). Bidirectional flow is observed in the main pulmonary artery (PA), with retrograde flow (arrow) from the ductus arteriosus (PDA).

among those serially studied (three with tricuspid dysplasia and one with Ebstein's malformation) had normal forward pulmonary artery flow by pulsed or continuous wave Doppler and color flow mapping. At serial follow-up study of these fetuses, however (at a mean gestational age of 34 weeks), there was retrograde ductal flow in association with the development of critical pulmonary stenosis in one and valvar pulmonary atresia in the three others (Fig. 4). All four had autopsy confirmation of a right ventricular outflow obstructive lesion or short segment pulmonary atresia. All four fetuses were also found to have a nontortuous ductus arteriosus, with an obtuse inferior angle at its junction with the descending aorta, suggesting the presence of normal anterograde flow from the ductus arteriosus to the aorta through most of gestation.

Clinical course in utero. On review of the clinical course of the 23 fetuses diagnosed with tricuspid valve disease and significant tricuspid regurgitation, excluding three cases of Ebstein's malformation with elective termination of pregnancy, we found the outcome of in utero tricuspid valve disease to be more dismal than what might have initially been predicted. Eleven (48%) of the 23 fetuses died in utero at a gestational age ranging from 21 to 38 weeks (mean 29), including 44% of the fetuses with Ebstein's anomaly, 43% of those with tricuspid dysplasia and both fetuses with an unguarded tricuspid orifice. Associated findings among these fetuses were hydrops fetalis in five, pulmonary atresia in two and atrial flutter in four.

Clinical course in neonatal period. Eight fetuses who had survived to delivery died within the first 2 weeks of life despite aggressive resuscitative and therapeutic efforts. Among the eight were 36% of the fetuses with Ebstein's anomaly and 43% with tricuspid dysplasia. Five of the eight had pulmonary stenosis or pulmonary atresia. All eight were delivered prematurely at a gestational age ranging from 30 to 37 weeks (mean of 35), including two with an induced delivery. Five neonates whose lesions did not require surgery and who were medically managed were difficult to ventilate adequately. Two of these neonates were in severe congestive heart failure and another was in atrial flutter. Three other neonates, two with pulmonary atresia and one with critical pulmonary stenosis, who had surgery for central shunt placement remained in severe cardiac failure and died 12 to 48 h postoperatively.

Survivors beyond the neonatal period. Among the 23 fetuses, there were only 4 who survived beyond the neonatal period. One of these infants with tricuspid dysplasia and pulmonary atresia was hypoxic on prostaglandin and underwent placement of a 4 mm modified Blalock-Taussig shunt at 10 h of age. She was discharged after a difficult 3 week course (requiring 10 days of mechanical ventilation and 17 days with supplemental oxygen) and died suddenly at 4 months of age despite an apparently functioning shunt. The three others who survive to date all were believed to have moderate Ebstein's anomaly at the postnatal echocardiographic study, and all demonstrated progressive clinical improvement beyond the immediate neonatal period. None of these three infants required prolonged ventilation or supplemental oxygen. One of the three infants also had pulmonary stenosis and underwent successful pulmonary balloon valvuloplasty in the neonatal period. She was weaned from oxygen at 5 days of age and now, at 5 years of age, this child is equal in size to her twin and has mild pulmonary stenosis, mild tricuspid regurgitation and a small patent ductus arteriosus. A second infant with Ebstein's anomaly had only mild cyanosis and Wolff-Parkinson-White syndrome by electrocardiography in the newborn period. At age 3 years, this child has no arrhythmias and remains on a prophylactic antiarrhythmic regimen. The last infant with Ebstein's anomaly was discharged without any problems after a 5 day nursery course with 2 days on supplemental oxygen. She is presently asymptomatic at 4 years of age.

Pulmonary hypoplasia. One additional finding among the fetuses in this series was a high incidence of pulmonary hypoplasia (23). This finding was established in 10 of 19 fetuses who died, with lung weights consistently nearly less than half of that expected for total body weight. Pulmonary hypoplasia was suspected clinically in two additional neonates without postmortem study, who could not be adequately ventilated and eventually died at <2 days of age. Only 40% of the fetuses (or infants) with autopsy confirmed or clinically suspected pulmonary hypoplasia had anatomic right ventricular outflow obstruction.

Discussion

Prenatal diagnosis of tricuspid valve disease. In our retrospective study, we have shown that two-dimensional echocardiography with high resolution imaging in the fetus permits description of tricuspid leaflet morphology, including proximal and distal attachments, for making the diagnosis of one of three types of tricuspid valve disease: Ebstein's anomaly, tricuspid valve dysplasia with normal proximal attachment of the leaflets and the extremely uncommon unguarded tricuspid valve orifice. Color flow mapping and spectral Doppler imaging provide information related to the presence of associated tricuspid regurgitation and aid in the identification of abnormal right ventricular outflow tract and pulmonary artery flow suggestive of pulmonary outflow obstruction, a commonly associated cardiac lesion, or poor right ventricular function. The finding of right atrial enlargement on an early sonogram should prompt the search for tricuspid valve abnormalities with tricuspid regurgitation and the presence or development of pulmonary atresia or stenosis. With the information provided, early detection of tricuspid valve disease should be possible so that the option of therapeutic abortion can be offered.

Development or progression of lesions in the second and third trimester. Although the majority of congenital heart lesions probably develop within the first 8 weeks of gestation, during the period of cardiac embryogenesis, some have suggested, with recent documentation of cases (24–29), that

certain cardiac lesions may be acquired or progress to a greater degree of severity later in utero. In 1984, Allan et al. (27) described a case of in utero progression of coarctation of the aorta. More recently, Todros et al. (29) described the development of pulmonary stenosis by 34 weeks of gestation in one fetus whose initial cardiac examination at 20 weeks of gestation was believed to be entirely within normal limits by two-dimensional and M-mode echocardiography. In the present study, we provide further evidence for the evolution of heart disease later in gestation. We have documented the development of pulmonary stenosis and atresia in fetuses who were diagnosed initially only with tricuspid valve disease and who by color and spectral Doppler imaging at the initial examination had normal forward pulmonary artery flow.

The appearance of the ductus arteriosus and the angle at which it joins the descending aorta have been thought (25,26) to provide clues as to the timing of the development of the right ventricular outflow obstruction with concomitant retrograde ductal flow. Our study provides support for this theory, with the four fetuses with documented late development of pulmonary obstruction having a normal-appearing ductus arteriosus joining the aorta at an obtuse inferior angle. This was also an observation made in the case documented by Todros et al. (29).

The etiology of the in utero acquired pulmonary obstruction in the presence of tricuspid valve disease is at present unknown. One might speculate that the development of pulmonary stenosis or atresia may in part be due to inadequate right ventricular forward flow. This concept may also be supported in the case of the fetus with left-sided Uhl's anomaly of the right ventricle (L-loop) and Ebstein's anomaly, with the aorta rather than the pulmonary artery affected.

Irrespective of the etiology, the potential for the development or significant progression of a primary or associated cardiac lesion in the mid and third trimester fetus poses a difficult problem for the fetal ultrasonographer. Because the in utero cardiac chamber and great artery growth progresses in part as a function of cardiac flow, a "normal" fetal echocardiographic examination early in the second trimester does not ensure absence of a serious cardiac lesion later in gestation or at term. In the presence of any fetal abnormality, especially tricuspid valve disease, it would seem unequivocally advantageous to serially monitor the fetus through to term.

Clinical course of fetuses with in utero tricuspid valve disease. The most significant finding in our collaborative review relates to the extremely poor outcome of fetuses diagnosed in utero with tricuspid valve disease. Of the 23 fetuses followed up, 48% had died in utero and 35% survived delivery only to die within the first 10 days of life, making the total mortality rate as high as 83%.

The high overall mortality rate observed in fetuses with tricuspid valve disease is similar to that associated with other forms of prenatally diagnosed heart disease (13,14,24); however, as yet, no study of prenatal heart disease has demonstrated such a high in utero mortality rate as observed in our series of fetuses, especially in the absence of other major congenital abnormalities. In an earlier study (14) of 29 fetuses with atrioventricular canal defect, although the neonatal mortality rate was 47%, there were only four deaths (27%) in utero. In another study (24) of seven cases with prenatally diagnosed pulmonary atresia and intact ventricular septum, only two did not survive to term, with four other deaths in the newborn period.

Although prior knowledge of the disease resulted in aggressive planning of resuscitative efforts, medical therapy and, when indicated, surgical management in the immediate neonatal period, the outcome of the fetuses with tricuspid valve disease who survived to delivery was still poor. Among those fetuses who died in the newborn period, there was a high incidence of massive cardiomegaly, congestive heart failure (62%) and pulmonary outflow obstruction (62%). Based on previous natural history studies (2–4,7,9), all three associated findings have been thought to confer a worse prognosis in the infant diagnosed with tricuspid valve disease and tricuspid regurgitation. Likewise, the presence of lung hypoplasia in the majority of infants who died in the neonatal period undoubtedly also contributed to the poor survival rate, making adequate ventilation difficult in the neonate with an already reduced arterial oxygen saturation due to right to left shunting. Appropriate treatment of this combination of heart and lung disease would require therapeutic planning aggressive enough to include extracorporeal membrane oxygenation support.

Given the relatively smooth neonatal courses, we suspect that the three surviving children have tricuspid valve disease that represents the milder spectrum of the disease encountered prenatally. In retrospect, however, the echocardiographic images of the tricuspid valve with significant tricuspid regurgitation and cardiomegaly observed in utero in these fetuses could not be readily distinguished from those whose course ended in neonatal death. The outcome of the fetuses who survive to delivery is probably best predicted on the basis of the early neonatal course and need for extensive medical intervention and potential surgical palliation.

Lung hypoplasia. As we recently demonstrated (23), pulmonary hypoplasia appears to be related at least in part to the presence of massive in utero cardiomegaly, with the heart occupying most of the intrathoracic space necessary for normal lung growth. Its association with congenital heart disease diagnosed in utero was first described (24) in several fetuses with the combination of pulmonary atresia and intact ventricular septum and a dilated right ventricle. Many of the cases in our previous series (23) did not have right-sided abnormalities with reduced pulmonary flow or decreased pulmonary artery size, and more than half of the cases in our present study did not have right ventricular outflow obstruction. We believe that changes in pulmonary flow and the space-occupying effect of the massive cardiomegaly itself may both be factors that contribute to lung hypoplasia. In support of the latter, the pulmonary findings described at

autopsy in our patients are similar to those described in the presence of diaphragmatic hernia, further suggesting a relation between available thoracic volume and lung development.

Conclusion. Although our collaborative study includes a group of patients that may have been selected because of more severe disease recognized and referred by outside obstetricians, it appears that the prognosis for fetuses with tricuspid valve disease and significant tricuspid regurgitation, including Ebstein's anomaly, tricuspid dysplasia and unguarded tricuspid valve orifice, diagnosed in utero is extremely poor. The information provided in this retrospective study is of significant importance in counseling parents about the expected outcome of their pregnancy and planning the most effective postnatal treatment in those fetuses who survive to delivery.

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