Pulmonary Atresia With Intact Ventricular Septum
Impact of Fetal Echocardiography on Incidence at Birth and Postnatal Outcome

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for the UK and Eire Collaborative Study of Pulmonary Atresia With Intact Ventricular Septum

Background—Fetal echocardiography is widely established in the United Kingdom for prenatal diagnosis of congenital heart disease. This may result in a substantial reduction in incidence at birth because of selected termination of pregnancy. The objective of this population-based study was to determine the incidence of pulmonary atresia with intact ventricular septum (PAIVS) at birth, the impact of fetal echocardiography on this incidence, and to compare the outcome of cases with and those without prenatal diagnosis.

Methods and Results—From 1991 to 1995, all infants born with PAIVS and all fetal diagnoses in the United Kingdom and Eire were studied. There were 183 live births (incidence 4.5/100 000 live births). The incidence was 4.1 cases per 100 000 live births in England and Wales, 4.7 in Scotland, 6.8 in Eire, and 9.6 in Northern Ireland (P = 0.01). There were 86 fetal diagnoses made at a mean of 22.0 weeks of gestation leading to 53 terminations of pregnancy (61%), 4 intrauterine deaths (5%), and 29 live births (34%). The incidence at birth would be 5.6 per 100 000 births in England and Wales, 5.3 in Scotland, and unchanged in Eire and Northern Ireland, if there were no terminations of pregnancy and assuming no further spontaneous fetal deaths (P = 0.28). An initial diagnosis of critical pulmonary stenosis was made in 6 cases, at a mean of 22.3 weeks of gestation with progression to PAIVS by 31.4 weeks. Probability of survival at 1 year was 65% and was the same for live-born infants whether or not a fetal diagnosis had been made.

Conclusions—PAIVS is rare, occurring in 1 in 22 000 live births in the United Kingdom and Eire. Termination of pregnancy has resulted in an important reduction in the live-born incidence in mainland Britain. (Circulation. 1998;98:562-566.)

Key Words: pulmonary heart disease n pulmonary atresia n echocardiography n diagnosis n pediatrics

Prenatal ultrasonography is widely established in the United Kingdom and is performed in >90% of pregnancies. In many regions this includes a detailed fetal anomaly scan performed between 16 and 20 weeks of gestation.1-3 Abnormalities in cardiac size, structure, and function are sought by imaging the cardiac 4-chamber view. It has been estimated that 15% to 25% of all cases of congenital heart disease (CHD) are detectable from this view,1,4 including nearly 60% of cases of complex CHD.5 When cardiac abnormalities are detected on the screening examination, a referral is made to a regional pediatric cardiologist for a detailed cardiac scan (fetal echocardiogram).1-5 Fetal echocardiography has been shown to be an accurate technique for the diagnosis of CHD, including pulmonary atresia with intact ventricular septum (PAIVS).6,7 Allan et al6 reported an incorrect or unconfirmed diagnosis in 96 of 1006 cases (7%), and most incorrect diagnoses were considered not to affect prognosis significantly. It has been suggested that prenatal echocardiography may, in time, cause a substantial reduction in the incidence of complex CHD seen at birth because of selected termination of pregnancies.6 The aims of this study were to ascertain, in a population-based review, the incidence of PAIVS at birth, the impact of fetal echocardiography on this incidence, and to assess the outcome for the fetus including a comparison of outcome for live-born infants with and those without a fetal diagnosis.

Methods
The United Kingdom and Eire Collaborative study of PAIVS is a multicenter, population-based study of all children born with PAIVS in the United Kingdom and Eire over a 5-year time period from January 1, 1991, to December 31, 1995. All fetal diagnoses of PAIVS, whose estimated date of delivery lay within that time frame, were also included. Data collection was retrospective from 1991 to 1993 and prospective from 1994 to 1995. Completeness of data collection was accomplished by a single investigator (P.E.F.D.) visiting on several occasions from 1993 to 1996 all the 17 centers for pediatric cardiology in the United Kingdom, and the single center in
TABLE 1. Regional Incidence of PAIVS and ‘Corrected Incidence’ Expected Assuming No Terminations of Pregnancy and No Additional Spontaneous Intrauterine Deaths

<table>
<thead>
<tr>
<th>Region</th>
<th>Incidence/100 000 Live Births</th>
<th>Corrected Incidence</th>
<th>Decrease in Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>England and Wales</td>
<td>4.1</td>
<td>5.6</td>
<td>27%</td>
</tr>
<tr>
<td>Scotland</td>
<td>4.7</td>
<td>5.3</td>
<td>12%</td>
</tr>
<tr>
<td>Northern Ireland</td>
<td>9.6</td>
<td>9.6</td>
<td>0%</td>
</tr>
<tr>
<td>Eire</td>
<td>6.8</td>
<td>6.8</td>
<td>0%</td>
</tr>
</tbody>
</table>

Eire (see Acknowledgments for Participating Institutions). Live-born infants with PAIVS were enrolled by direct inspection of local databases, admission records, and echocardiography log books. Fetal diagnoses were obtained by direct inspection of fetal echocardiography databases and log books. Regional pathologists were contacted to identify unrecognized cases of PAIVS among stillbirths and unexplained postnatal deaths. Cases were included when they had PAIVS without other complex cardiac abnormalities, though cases of tricuspid valvar dysplasia or Ebstein’s malformation coexisting with PAIVS were included. Cases were excluded if they were born outside the United Kingdom and Eire. Fetal diagnoses of critical pulmonary stenosis were only included when there was documentation of progression to PAIVS. The outcome for each fetal diagnosis was ascertained and recorded. All data were stored on a relational database in coded fashion (Filemaker Pro 3.0, Claris Corp). This was an observational study, and no attempt was made to influence management of individual cases.

Statistical Analysis

Categorical data were compared with the use of Pearson’s χ² test with Yates’ correction as appropriate when expected values were small. The Mann-Whitney U test was used to compare nonparametric data. Probability of survival was calculated according to the method of Kaplan and Meier, and survival curves were compared with the use of the log-rank test (Statview 4.1, Abacus Concepts). Values of P<0.05 were considered statistically significant.

Results

Incidence

There were 183 live births with PAIVS for the 5-year period of 1991 to 1995. The total number of births during this time in the United Kingdom and Eire was 4 068 145, giving an incidence of 4.5 per 100 000 live births. The incidence of PAIVS at birth was 4.1 cases per 100 000 live births in England and Wales, 4.7 in Scotland, 6.8 in Eire, and significantly higher at 9.6 in Northern Ireland (P=0.01) (Table 1). There were 86 diagnoses made in fetal life at a mean of 22.0 weeks of gestation (SD 4.6, range 15 to 37). The proportion of total cases of PAIVS that were diagnosed in fetal life was 43% in England and Wales, 18% in Scotland, and 0% in Northern Ireland and Eire. Outcome for the fetuses with antenatal diagnosis of PAIVS comprised 53 terminations of pregnancy (61%), 4 intrauterine deaths (5%), and 29 live births (34%) (Table 2). Had there been no terminations of pregnancy (and assuming that no further intrauterine deaths would have occurred in the pregnancies that were terminated), the incidence of PAIVS at birth would be 5.6 per 100 000 births in England and Wales, 5.3 in Scotland, and unchanged in Eire and Northern Ireland, where there were no terminations of pregnancy (Table 1). The difference in incidence between England and Wales and Northern Ireland then narrows and no longer reaches statistical significance (P=0.28).

Table 3 shows the trend in terminations of pregnancy over the period of study for England, Wales, and Scotland only. The number of terminations as a proportion of the number of fetal diagnoses made was fairly constant over the period of study. The decrease in incidence at birth that occurred as the result of terminations of pregnancy (again assuming no further fetal losses) ranged from 12.5% in 1991 (when there were fewest fetal diagnoses) to a peak of 37% in 1993.

Morphological Features

Ebstein’s malformation coexisting with PAIVS was diagnosed prenatally in 9 of 86 (10%) cases. An additional 11 of 86 cases were labeled prenatally as having severe tricuspid regurgitation caused by “tricuspid valvar dysplasia” without Ebstein’s malformation in addition to PAIVS (Figure 1). An initial diagnosis of critical pulmonary stenosis had been made in 6 of 86 (7%) cases, at a mean gestation of 22.3 weeks (range 19 to 28). Progression to PAIVS was documented at a mean of 31.4 weeks of gestation (range 24 to 40). All 6 infants were live-born, and absence of antegrade flow across the atretic valve was confirmed in all cases. Five infants were diagnosed prenatally as having small muscular ventricular septal defects. Only 1 case was confirmed by postnatal echocardiography (a tiny apical defect). In 3 of the 4 remaining cases, postnatal echocardiography and angiography demonstrated fistulous communications from the right ventricle to the coronary arteries, which may have been the cause of the disturbance in color flow seen in the region of the muscular ventricular septum on the prenatal echocardiogram. Insufficient data were recorded from fetal echocardiograms to allow reporting of tricuspid valvar diameters or right ventricular cavity size or to allow distinction (in most cases) of membranous from muscular atresia. Among the cases resulting in termination of pregnancy or spontaneous intrauterine death (n=57), autopsy examination of the fetal heart was

TABLE 2. Outcome After Fetal Diagnosis of PAIVS With and Without Ebstein’s Malformation

<table>
<thead>
<tr>
<th>PAIVS</th>
<th>PAIVS/Ebstein’s</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terminations of pregnancy</td>
<td>45</td>
<td>8</td>
</tr>
<tr>
<td>Intrauterine deaths</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Live born</td>
<td>28</td>
<td>1</td>
</tr>
<tr>
<td>Total fetal diagnoses</td>
<td>77</td>
<td>9</td>
</tr>
</tbody>
</table>

TABLE 3. Impact of Termination of Pregnancy on Number of Live Births With PAIVS for Each Year of Study in England, Wales, and Scotland Only

<table>
<thead>
<tr>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal diagnosis of PAIVS</td>
<td>11</td>
<td>19</td>
<td>18</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>Pregnancies terminated</td>
<td>5 (45%)</td>
<td>12 (63%)</td>
<td>14 (78%)</td>
<td>12 (60%)</td>
<td>10 (56%)</td>
</tr>
<tr>
<td>Decrease in birth incidence</td>
<td>12.5%</td>
<td>24%</td>
<td>37%</td>
<td>27%</td>
<td>29%</td>
</tr>
</tbody>
</table>

Analysis assumes no further intrauterine deaths would have occurred if no terminations had been performed.
performed in 41 (72%). This confirmed the diagnosis of PAIVS in all cases.

PAIVS was associated with Down’s syndrome in 3 cases. In 2 of these cases, a fetal diagnosis of Down’s syndrome and PAIVS was made and led to termination of pregnancy. In 1, there was a severely hypoplastic and hypertrophied right ventricle and in the other, PAIVS was associated with a dilated right atrium and right ventricle with Ebstein’s malformation of the tricuspid valve with severe valvar regurgitation. Both fetuses also had pericardial effusions. In the third case, also with Ebstein’s malformation and dilated right heart, a prenatal diagnosis of Down’s syndrome was not made and the infant was live-born.

**Prenatal Intervention**

Two patients had prenatal cardiac interventions. One of these cases has been previously described. This involved a cardiocentesis by direct transventricular puncture at 31 weeks of gestation, which revealed a ratio of pressure between the right and left ventricles of 1.4:1. Injection of saline failed to demonstrate forward flow across the pulmonary valve and, with an unfavorable position of the fetus, attempted valvar perforation and dilation was not performed. The second prenatal cardiac intervention was an attempted radiofrequency perforation of the pulmonary valve at 23 weeks of gestation, unsuccessful because of inadequate positioning of the wire in the right ventricular outflow tract. This was repeated at 26 weeks, and the valve was successfully perforated and this was followed by balloon angioplasty. This resulted in antegrade pulmonary blood flow. After birth, the valve had become almost atretic again, though a 0.025-inch guide wire could be passed into the pulmonary artery. It was not possible, however, to pass a catheter across the valve, and surgical intervention was carried out (personal communication, Dr J. Wright, Birmingham Children’s Hospital).

**Outcome**

The 4 intrauterine deaths occurred at 31, 32, 32, and 32 weeks of gestation. The causes for these are unknown. Among the 53 pregnancies undergoing termination, 2 had abnormal fetal karyotypes (both trisomy 21) (see above). No other chromosomal abnormalities were documented before birth.
Infants were born at comparable gestational age, irrespective of whether fetal diagnosis had been made (mean [SD] 38.2 [2.3] weeks vs 38.7 [2.3] for infants with or those without a fetal diagnosis, respectively, $P=0.307$). Fetuses with prenatal diagnosis were no more likely to be delivered by cesarean section than their counterparts without fetal diagnosis (4/25, 16% vs 42/134, 31%, respectively, $P=0.12$; mode of delivery unknown in 24 cases). Twenty-one (72%) of the live-born infants with a prenatal diagnosis were delivered in proximity to a center for pediatric cardiology, and all were commenced on an infusion of prostaglandin E1 (to maintain patency of the arterial duct) in the first few hours of life. Among infants without a fetal diagnosis, only 19% were born in, or nearby, a center for pediatric cardiology ($P<0.0001$). Of patients without prenatal diagnosis, recognition of cyanotic heart disease was usually rapid (mean time to commencement of prostaglandin infusion 0.9 days, range 0 to 32; mean time to transfer to a cardiac unit 2.2 days, median 1 day, range 0 to 45). However, 7 of the 154 infants (4.5%) without a fetal diagnosis of PAIVS were discharged home from the hospital without a diagnosis of heart disease. They were subsequently readmitted after development of severe cyanosis or shock. All 7 infants were successfully resuscitated and survived to undergo initial palliation. One infant had an arterial pH of 6.9 secondary to severe hypoxemia but had no neurological deficit at latest follow-up.

Survival comparison was made between the 29 live-born cases with prenatal diagnosis of PAIVS and the remaining 154 live-born infants who were not diagnosed prenatally. Probability of survival was 65% (95% confidence interval [CI] 47% to 82%) at 1 year and 59% (95% CI 39% to 78%) at 2 years for infants with a prenatal diagnosis (Figure 2). This was similar to the group without prenatal diagnosis (1-year survival, 65% [95% CI 58% to 73%] and 2-year survival, 64% [95% CI 56% to 72%], log-rank, $P=0.576$). The morphological features of these 2 groups, as determined at birth, were also compared. No differences were found in the proportion of infants with the following features: membranous versus muscular atresia ($P=0.230$); obliteration by muscular overgrowth of either the apical and outlet components, the apical component alone, or the presence of 3 well-developed ventricular components (often described as so-called unipartite, bipartite, or tripartite ventricles) ($P=0.796$); and the presence or absence of Ebstein’s malformation ($P=0.271$), coronary-right ventricular fistulas ($P=0.792$), or coronary arterial stenoses ($P=0.190$). There were also no differences between the 2 groups for the following continuous variables measured by cross-sectional echocardiography in the apical 4-chamber view: $z$-score for tricuspid valvar diameter, $P=0.896$, and $z$-score for right ventricular inflow dimension (mid annulus to apex), $P=0.630$.

Discussion

We have demonstrated that the incidence of PAIVS in the United Kingdom and Eire for the 5-year period 1991 to 1995 was 4.5 cases per 100 000 live births. In the New England Infant Cardiac Program, the incidence was 7.1 cases per 100 000 live births.10 The Baltimore-Washington Infant study reported an incidence of 8.1 per 100 000 live births for the period 1981 to 1989.11 We have also demonstrated regional variation, with an incidence twice as high in Northern Ireland. CHD has previously been reported as being more common in Northern Ireland.12 At least some of the difference in the current study, however, is explained by the high rate of termination of pregnancy in mainland Britain after fetal echocardiographic diagnosis. Indeed, almost two thirds of women elected to terminate their pregnancy after prenatal diagnosis of this serious congenital cardiac malformation. This proportion is similar for other complex lesions reported in the United Kingdom.13 For the 5 years of the study, termination of pregnancy in mainland Britain resulted in a decrease in incidence at birth of 26%. This calculation assumes that all pregnancies terminated would have progressed to term. In reality, this assumption is unlikely to be valid. We speculate that termination of pregnancy would be most likely to be carried out for fetuses showing the greatest hemodynamic compromise (such as those with severe tricuspid regurgitation and fetal hydrops). The study was not able to provide the cause of the 4 intrauterine deaths. Furthermore, the calculation also assumes that any pregnancies with fetal critical pulmonary stenosis that may have been terminated would not have progressed to PAIVS. Even allowing for these assumptions, it appears that fetal echocardiography is having an important impact on birth incidence of PAIVS.

Abu-Harb and colleagues4 estimated that fetal echocardiographic screening with the 4-chamber view will decrease the overall incidence of CHD at birth by only 2%. This reduction assumes that only 15% of CHD is readily detectable from the 4-chamber view, that the detection rate is 20%, and that the termination rate is 67%. The authors did comment that reductions could be higher for complex lesions. The overall detection rate in our study was considerably higher, at 41% (86/211) for mainland Britain or 36% (86/240) for the United Kingdom and Eire combined. This may be because this lesion is more readily detectable on a 4-chamber view than other lesions.13 Increasing experience with fetal cardiac scanning by obstetric ultrasonographers may increase the frequency of antenatal diagnosis. The observation that this disease may evolve from critical pulmonary stenosis, and the potential for late growth failure of the right ventricle in the latter half of pregnancy, suggest that a single scan at 16 to 20 weeks of gestation may not be adequate to identify all cases of this condition.
The association of PAIVS and Down’s syndrome is very rare but occurred in 3 of 240 (1.3%) cases in this study. Van Praagh et al.14 list a single patient with Down’s syndrome and pulmonary atresia with intact ventricular septum in the Cardiac Registry of the Children’s Hospital of Boston (among 100 cases of Down’s syndrome with CHD).

The decision to terminate a pregnancy will be influenced by a variety of factors other than the anticipated prognosis. Paramount among these will be the cultural and religious values of the family and community. Even when termination of pregnancy is not a consideration, fetal echocardiographic diagnosis has several other implications for management of the pregnancy and the newborn infant. Prenatal scanning has clearly affected the choice of hospital for delivery, with most infants in the current study being born in, or near, referral centers for pediatric cardiology. Furthermore, those infants with a prenatal diagnosis received earlier institution of prostaglandin E1 infusion before closure of the arterial duct. Among infants without prenatal diagnosis, almost 5% were discharged from their maternity unit without a diagnosis of heart disease. Such infants are at risk for the development of profound cyanosis before return to hospital and are at risk for sudden infant death in the community. We are not aware of any instances of sudden infant death secondary to ductal closure in newborns with PAIVS during our period of study. It is possible, however, that such cases might be missed, because inquires were made only of regional pathology services specializing in pediatric pathology. No attempt was made to survey all pathologists in the United Kingdom and Eire who might perform a postmortem examination on an infant dying unexpectedly at home. Although one might anticipate that fetal diagnosis might improve neonatal outcome because of earlier appropriate therapeutic intervention, we have failed to demonstrate an advantage in terms of survival for live-born infants with a prenatal diagnosis. The spectrum of severity of PAIVS was similar whether prenatally diagnosed or not. This might account for the similar outcome for the 2 groups. Other less tangible benefits of prenatal diagnosis have been suggested. It may allow parents to “prepare” themselves psychologically, thus allowing a more cognitive and less emotional approach to the decisions to be made after birth. In addition, there is the potential for fetal intervention. If antegrade flow across the pulmonary valve could be achieved (and maintained) before the development of severe hypoplasia of the right ventricle, then there may be a greater chance of achieving successful biventricular repair. Fetoscopic and open transumbilical cardiac catheterization has been performed on fetal sheep with successful balloon valvoplasty of surgically created supravalvar pulmonary stenosis.15 Such feasibility studies are in their infancy, and much more experimental work will be required before such prenatal interventions can be routinely recommended in clinical practice. In the only case in our study in which fetal valvotomy was successfully achieved, virtual atresia had recurred by the time of birth.

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References

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