ORIGINAL ARTICLE

Prenatal diagnosis of pulmonary atresia: impact on clinical presentation and early outcome

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Aim: The impact of prenatal diagnosis on morbidity and mortality for certain types of congenital heart disease (obstructive left heart lesions and transposition of the great arteries) is well established. No data are available for lesions with duct dependent pulmonary flow. We aimed to assess the impact of prenatal diagnosis of pulmonary atresia on clinical presentation and neonatal outcome.

Method: Fifty-eight newborns with pulmonary atresia presenting to our centre were identified retrospectively between 1997 and 2004 (prenatal diagnosis $n=37$, postnatal $n=21$). Anatomical sub-types included intact ventricular septum (PAIVS, $n=33$) and ventricular septal defect (PAVSD, $n=25$); those with more complex anatomy were excluded.

Results: After adjusting for anatomical sub-type, postnatally diagnosed infants were significantly more hypoxic at presentation (mean oxygen saturation 65% vs 84%). However, they presented early (median age 1 day) and prostaglandin E was initiated promptly (median 3 hours) with rapid improvement of oxygen saturations (interaction $p<0.001$). This resulted in no appreciable differences in terms of pH, base deficit, blood pressure or heart rate between the groups by the time of the first catheter/surgical intervention. Postnatal infants did not differ in terms of length of intensive care unit ($p=0.18$) or hospital stay ($p=0.86$), incidence of complications ($p=0.72$), or mortality ($p=0.77$). Multivariable analysis revealed a positive association between occurrence of complications and both degree of cyanosis at presentation (rather than postnatal diagnosis per se) and anatomy (PAIVS).

Conclusion: Postnatal diagnosis of pulmonary atresia is associated with greater cyanosis at presentation. However this does not translate into greater neonatal morbidity or mortality provided that early recognition and prompt initiation of prostaglandin E therapy occur.

The accuracy of prenatal diagnosis for congenital heart disease is well established.^{1,2}

Most congenital heart defects, including right-sided lesions, can be diagnosed prenatally.^{1–4}

Recent data suggest benefit from prenatal diagnosis on the condition at presentation, postnatal morbidity and mortality for several cardiac lesions including hypoplastic left heart syndrome (HLHS),^{5–7} coarctation of the aorta⁸ and transposition of the great arteries (TGA).^{9,10} However, there has been no perinatal study on infants with duct dependent pulmonary blood flow, evaluating whether prenatal diagnosis is associated with better condition at presentation and improved early outcome compared to those diagnosed postnatally.

The aim of this paper is to report on a cohort of infants with pulmonary atresia, and to compare the clinical profile of those who were diagnosed prenatally with those in whom the diagnosis was made postnatally. We hypothesized that infants who were diagnosed prenatally would present in better condition and have a lower mortality and morbidity than those diagnosed postnatally. A second aim of the study was to analyse this patient group for other factors which might impact on mortality and morbidity.

METHODS

Patient selection

We identified all infants in whom a diagnosis of pulmonary atresia was made prenatally or postnatally at Guy's and St Thomas' Hospital, London, over an 8 year period between January 1997 and December 2004. Case ascertainment was from the hospital paediatric intensive care unit, neonatal intensive care unit, cardiac catheterisation laboratory, surgical

and fetal cardiology databases, on which data are entered prospectively.

We included infants with usual atrial arrangement, concordant atrioventricular connections and normally related great arteries, who had pulmonary atresia with either a ventricular septal defect (PAVSD) or an intact ventricular septum (PAIVS) and duct dependent pulmonary flow. Infants with alternative sources of pulmonary blood flow such as major aortopulmonary collateral arteries were excluded. Those with more complex congenital heart disease, for example laterality defects or discordant atrioventricular connections, were excluded because it was felt that associated lesions such as anomalous pulmonary venous drainage or Ebstein's anomaly might dramatically alter the clinical profile of affected infants.

Any infant with antegrade flow across the pulmonary valve was excluded. None of the prenatally diagnosed infants underwent fetal interventions.

The postnatal management approach to infants with PAVSD and PAIVS is different. The priority in PAVSD without aortopulmonary collateral arteries is to maintain adequate pulmonary blood flow with an anticipation of a biventricular repair in the longer term. For infants with PAIVS, factors such as the size of the tricuspid valve, right ventricle and type of pulmonary atresia (muscular versus "membranous") influence the management approach. However, in terms of presentation, those infants meeting our inclusion criteria present with cyanosis and a duct dependent pulmonary circulation. Where

Abbreviations: ANCOVA, analysis of covariance; HLHS, hypoplastic left heart syndrome; ICU, intensive care unit; PAIVS, pulmonary atresia with an intact ventricular septum; PAVSD, pulmonary atresia with ventricular septal defect; TGA, transposition of the great arteries

necessary we have accounted for the two anatomic subtypes in the statistical analysis.

Study variables

The medical records of all infants were reviewed. For live born infants the length of intensive care unit (ICU) and hospital stay were recorded for both prenatal and postnatal groups. The haemodynamic data, PaO₂, arterial saturations and acid-base status were recorded at presentation as well as immediately before and after initial intervention. Blood lactate levels at presentation were not available on a number of patients who presented postnatally and therefore lactic acid status was not assessed. To evaluate the morbidity, we recorded the number of patients who presented one or more of the following complications: necrotising enterocolitis (requiring at least a week's course of intravenous antibiotics and parenteral nutrition), blood stream infection, cardiac arrest, cerebral haemorrhage, seizures and renal impairment requiring dialysis. In addition, prolonged total length of inotropic support and mechanical ventilation of >7 days were considered as adverse outcomes.

Statistical analysis

Group continuous data were analysed using either Mann Whitney or unpaired t-tests after inspection of the raw data via histograms and normal probability plots. Data are reported as median (interquartile range) or mean (standard deviation). Group categorical data were examined using the χ^2 -squared test and, when significant, reported with odds ratios and 95% confidence intervals.

Temporal data (change in physiologic, and laboratory variables between presentation and intervention) were analysed using two-way, repeated measures analysis of covariance (ANCOVA), with anatomical subgroup as the covariate (intact septum vs ventricular septal defect). This approach takes account of, and adjusts for the different proportions of anatomical subgroup within the prenatal and postnatal groups. As there were only two time points, post hoc testing was not undertaken.

ANCOVA p values are expressed for time, group, and time-group interaction effects. Interpretation of a significant p value for each effect is as follows: (a) time, there was a significant change in the parameter over time for the groups as a whole; (b) group, there was a significant difference between the two groups taking all time points into account; (c) time-group interaction, there was a difference in the parameter's rate of change over time between the two groups.

A logistic regression model was constructed using a forward stepwise approach to investigate variables associated with outcome (death, major complications, prolonged ICU and hospital stay). Prolonged ICU and hospital stay were defined as greater than ten and thirty days, respectively. This represented the upper quartile for each entity, and was justified on the basis of a clear bi-modal distribution for stay seen in the histograms for each. Independent categorical variables included: time of diagnosis (postnatal vs prenatal), anatomical group (intact septum versus ventricular septal defect), blood stream infection, weight <2 kg, significant hypoxia at presentation (oxygen saturation <70%), acidosis and prolonged prostaglandin use (>7 days). Independent continuous variables included heart rate, mean blood pressure, pH, base deficit, Pco₂, oxygen saturation (all at presentation), total days on prostaglandin, mean daily dose and maximum dose of prostaglandin.

In all cases a p value of <0.05 was regarded as significant. Statistical analyses were performed using SPSS 12.0 (SPSS Inc, Chicago, Illinois).

RESULTS

Patient characteristics

A total of 85 patients were diagnosed with either PAIVS or PAVSD during the study period. In all, 64 of these were diagnosed prenatally, of whom 25 sets of parents elected to terminate the pregnancy and there were two spontaneous intra-uterine deaths. Nine terminations were for PAVSD of whom none had extracardiac structural malformations but four had chromosome 22q11 deletions. Altogether 16 terminations were for PAIVS of whom one had pleural effusions and there were no documented karyotypic abnormalities.

There were 58 live born patients with pulmonary atresia identified over the study period with median (interquartile) gestational age and birth weight of 38 weeks (36–40 weeks) and 3.1 kg (2.7–3.3 kg) respectively. In all 37 patients were diagnosed prenatally and 21 postnatally (fig 1). Twenty-five prenatally diagnosed infants had an intact ventricular septum and 12 had an associated ventricular septal defect, whereas 8 of the postnatally diagnosed infants had an intact ventricular septum and 13 had an associated ventricular septal defect. Four patients had a 22q11 deletion (all with PAVSD); one patient had trisomy 21 and one Klinefelter syndrome. None of the patients had any other structural extracardiac malformations. The duration of follow-up of survivors ranged from 12 months to 5 years.

Interventions and mortality

The interventions which the live born infants underwent are shown in fig 1. Seven patients died in the neonatal/early infancy period (table 1): two with necrotising enterocolitis, one with Klebsiella sepsis, two with myocardial failure and two with pulmonary overcirculation. Four patients were diagnosed prenatally and three were diagnosed postnatally. The survival to 28 days was 91% (53/58 patients), (95% CI 81–97%) and at one year 86% (50/58 patients), (95% CI 75–94%).

Morbidity

Overall, nineteen patients experienced at least one major complication; of these five experienced only one complication, nine experienced two, and five experienced three or more complications. The numbers for each major complication were as follows:

Blood stream infection (n = 8), necrotising enterocolitis (n = 7), cardiac arrest (n = 5), renal impairment requiring dialysis (n = 2), cerebral haemorrhage (n = 2), seizures (n = 4), need for inotropic support >24 h (n = 13), prolonged mechanical ventilation >7 days (n = 11).

Subgroup analysis: presenting features of prenatal versus postnatally diagnosed patients

Postnatally diagnosed patients were more likely to have an associated ventricular septal defect (χ^2 4.75, p = 0.03, odds ratio 3.39, 95% CI 1.11 to 10.31). However this discrepancy in the proportions of anatomical sub-group between prenatally and postnatally diagnosed infants was accounted for in the subsequent statistical analyses.

Haemodynamic, arterial oxygen saturation and blood gas parameters for the two groups were compared during the time interval between presentation and the first interventional procedure (table 2). After adjustment for anatomical subgroup, postnatally diagnosed infants were significantly more hypoxic at presentation (mean oxygen saturation 65% versus 84%, p<0.001). However, postnatally diagnosed patients presented early, at a median age of 1 day, (IQR 0.75–2 days), and transfer to our centre took place swiftly, within a median of 8 hrs (IQR 7–9 h). Initiation of prostaglandin therapy was prompt once congenital heart disease was suspected, (median

Figure 1 Early interventions according to method of presentation (prenatal vs postnatal) and anatomical sub-type. Several infants required a second intervention within the neonatal period; these are shown in the lowest tier. Abbreviations: PAIVS, Pulmonary atresia with intact ventricular septum; PAVSD, Pulmonary atresia with ventricular septal defect; PDA, patent ductus arteriosus; RFP, radiofrequency perforation of the pulmonary valve; BTS, Blalock-Taussig shunt; BAS, balloon atrial septostomy.

of 3 h, IQR 2–6 h) and improvement in cyanosis occurred rapidly after commencement of prostaglandin infusion, such that there was no appreciable difference between the two groups by the time the first intervention was performed (fig 2).

Since postnatally diagnosed patients presented both later and more cyanosed, they received a higher maximal dose of prostaglandin E: 20 (10 to 30) ng/kg/min versus 10 (5 to 10) ng/kg/min ($p = 0.02$). The postnatal group underwent the first interventional procedure at a median time of 5 days post delivery (IQR day 3 to 17) compared to day 3 for the prenatal group (IQR day 2 to 4), ($p = 0.03$). There were no haemodynamic differences between the groups, although postnatal patients demonstrated a trend towards higher blood pressure (group $p = 0.058$); however the magnitude was small (mean overall difference of 3.0 mm Hg). There were no obvious differences between groups in terms of both pH and base deficit, although pH improved with time in both groups (table 2).

The overall median (interquartile) length of stay in the ICU was 6 (4 to 10) days and hospital was 18 (11 to 30) days. The two patient groups did not differ in terms of length of intensive care unit ($p = 0.18$) or hospital stay ($p = 0.86$), incidence of complications ($p = 0.72$), or mortality ($p = 0.77$).

Subgroup analysis: prediction of outcome

Factors associated with adverse outcome were investigated via a logistic regression model.

The only independent predictor for death was the presence of blood stream infection (adjusted OR 6.9, 95% CI 1.2 to 40.0). Postnatal diagnosis was not a predictor for any adverse outcome.

Factors associated with occurrence of a major complication included significant cyanosis on presentation (oxygen saturation

less than 70%), (adjusted OR 4.3, 95% CI 1.1 to 18.7) and intact ventricular septum (adjusted OR 6.8, 95% CI 1.6 to 29.3). All patients who developed necrotising enterocolitis had an intact septum. No factor reliably predicted prolonged ICU or hospital stay.

DISCUSSION

Early studies examining the value of prenatal diagnostic ultrasound screening for all types of congenital anomaly, fetal growth disorders and placental abnormalities failed to show a positive effect on perinatal outcome.^{1–11} However, more recent work has demonstrated benefit from prenatal diagnosis of congenital heart disease in terms of condition at presentation, morbidity, mortality, surgical outcome and neurodevelopmental outcome.^{5–10} Lesions examined to date have included left-sided anomalies (hypoplastic left heart, coarctation) and transposition of the great arteries.^{5–10} Until now, no study has reported on the impact of prenatal diagnosis for infants with duct-dependent pulmonary blood flow.

We limited our study to two major morphologic groups: PAIVS and PAVSD. This was to minimise the effects of confounding variables associated with more complex lesions (for example anomalous pulmonary venous drainage seen with laterality defects). Given the size of the dataset, this would permit meaningful statistical analyses to be undertaken. The incidence of PAIVS has been reported to be between 4.5–8 cases per 100 000 live births,^{3–12} whereas PAVSD occurs approximately in 10.0/100,000 live births.¹² Prenatal detection is feasible for both PAIVS and PAVSD, although fewer babies with PAVSD appear in our prenatal group. This is likely to be because the four chamber screening view of the heart is typically normal in PAVSD and abnormal in PAIVS. UK national data, between 1993 and 1995, confirmed a prenatal

Table 1 Characteristics of nonsurvivors

Anatomical subtype	Diagnosis	Procedure	Time of death (day of life)	Cause of death
PAIVS	Postnatal	RFP/PDA stent	D2	Pulmonary overcirculation
PAIVS	Postnatal	NIL	D7	Myocardial failure
PAVSD	Postnatal	Complete repair	D34	Myocardial failure
PAVSD	Prenatal	BTS	D6	Pulmonary overcirculation
PAIVS	Prenatal	BTS	D17	Necrotising enterocolitis
PAIVS	Prenatal	NIL	D3	Necrotising enterocolitis
PAIVS	Prenatal	RFP	D33	Klebsiella sepsis

PAIVS, Pulmonary atresia with intact ventricular septum; PAVSD, Pulmonary atresia with ventricular septal defect; PDA, patent ductus arteriosus; RFP, radiofrequency perforation; BTS, Blalock-Taussig shunt; NEC, necrotising enterocolitis.

Table 2 Haemodynamic, arterial oxygen saturations and blood gas results for prenatally and postnatally diagnosed patients

Variable	Group	Presentation	Preintervention	p Time	p Group	p Interaction
Heart rate (bpm)	Postnatal	143.1 (3.0)	135.5 (2.4)	0.32	0.13	0.06
	Prenatal	134.7 (2.2)	135.9 (1.8)			
Mean blood pressure (mm Hg)	Postnatal	48.3 (1.7)	49.7 (1.5)	0.68	0.06	0.99
	Prenatal	45.3 (1.3)	46.6 (1.1)			
arterial oxygen saturation (%)	Postnatal	65.5 (3.0)	83.1 (1.5)	<0.001	<0.001	<0.001
	Prenatal	84.7 (2.2)	87.0 (1.2)			
arterial pH	Postnatal	7.32 (0.02)	7.40 (0.01)	0.01	0.48	0.14
	Prenatal	7.33 (0.01)	7.36 (0.01)			
Base deficit (meq/l)	Postnatal	-3.4 (0.7)	-1.5 (0.6)	0.88	0.98	0.07
	Prenatal	-2.4 (0.6)	-2.5 (0.5)			
pCO ₂ (kPa)	Postnatal	5.5 (0.3)	4.9 (0.2)	0.006	0.23	0.72
	Prenatal	5.9 (0.2)	5.2 (0.2)			

The p values are calculated using analysis of covariance and represent time, group and interaction values. The covariate is anatomical subgroup (ventricular septal defect vs intact septum). Data are mean, (SEM).

diagnostic rate of only 10% for PAVSD, compared to 55% for PAIVS.¹³ Although these two groups are managed differently after birth, they share the feature of duct dependent pulmonary blood flow and statistical analysis via ANCOVA permitted us to take account of morphology and analyse groups separately where appropriate.

Our primary hypothesis was that prenatally diagnosed infants would have lower mortality and fewer complications than those identified postnatally; however this was not the case. Prenatal and postnatal groups had a similar death rate (4/37 vs 3/21), with no statistical difference in terms of length of stay in either the intensive care unit ($p=0.18$) or hospital ($p=0.86$). Indeed, the only independent predictor for death was the presence of infection, whereas factors associated with occurrence of a major complication included intact ventricular septum and significant cyanosis (oxygen saturation less than 70%) at presentation. Thus, degree of cyanosis at presentation and anatomical subtype (PAVSD vs PAIVS) rather than prenatal diagnosis appear to be the important factors. Furthermore, after adjustment for anatomical sub-type, the postnatal group, although cyanosed at presentation, improved rapidly after initiation of prostaglandin E therapy, such that

there were no discernable differences in haemodynamic and metabolic parameters by the time of first intervention.

The apparent lack of benefit from prenatal diagnosis in this study as compared to prior studies may be explained by the type of lesion. Previous studies have examined either duct-dependant *systemic* blood flow (hypoplastic left heart syndrome, coarctation of the aorta) or mixing lesions (transposition of the great arteries). In the case of the former, decompensation occurs as a result of reduced systemic blood flow, which may evolve over days. As a consequence, organ dysfunction may be well established by the time clinical signs are apparent, and are unlikely to resolve with prostaglandin E therapy alone. With mixing lesions, an emergency intervention (eg, septostomy) may also be necessary, which typically cannot be performed at the referring centre. In comparison, our study examined duct dependent pulmonary flow. Here cyanosis is the cardinal presenting sign, it is likely to become apparent soon after constriction of the arterial duct, systemic blood flow is maintained, and prostaglandin E therapy is likely to restore adequate systemic oxygen delivery.¹⁴ This is consistent with our findings, where postnatally diagnosed infants presented early (median age 1 day), and prostaglandin E was initiated promptly (median 3 h).

Two limitations of this study deserve mention. (1) Our tertiary centre is located within a geographically confined area with high population density. As outlined above, infants

Figure 2 Arterial oxygen saturations at presentation and prior to first intervention. Data are mean, error bars SEM.

What is already known on this topic

- Prenatal diagnosis of congenital heart defects by ultrasound is well established.
- Fetal diagnosis of transposition of the great arteries and left heart obstruction reduces postnatal morbidity and mortality.

What this study adds

- Prenatal diagnosis of pulmonary atresia is associated with improved oxygen saturations at presentation
- Diagnosis of pulmonary atresia during fetal life does not improve short-term morbidity or mortality compared to babies diagnosed postnatally.

presented early, prostaglandin was commenced rapidly, and admission to the tertiary centre occurred promptly (median 8 h). It might be that if referral centres were more geographically remote, with fewer local facilities, then a larger impact of prenatal diagnosis would have been observed, but this remains speculative.

(2) This study has examined short-term morbidity. We did not investigate other longer-term morbidity such as neurological development.

CONCLUSION

Prenatal diagnosis of pulmonary atresia results in improved oxygenation at presentation. However, postnatally diagnosed infants have the potential to improve rapidly, provided that their condition is diagnosed early and prostaglandin E therapy is instituted promptly. No difference was observed in the short-term mortality and morbidity between the prenatal and postnatal groups.

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REFERENCES

- 1 **Allan LD**. Early detection of congenital heart disease in prenatal life. *Clin Obstet Gynaecol* 1983;**10**:507-14.
- 2 **Allan LD**, Sharland GK, Milburn A, *et al*. Prospective diagnosis of 1006 consecutive cases of congenital heart disease in the fetus. *J Am Coll Cardiol* 1994;**23**:1452-58.
- 3 **Daubeney PEF**, Sharland GK, Cook AC, *et al*. Pulmonary atresia with intact ventricular septum: Impact of fetal echocardiography on incidence at birth and postnatal outcome. *Circulation* 1998;**98**:562-66.
- 4 **Maeno YV**, Boutin C, Hornberger LK, *et al*. Prenatal diagnosis of right ventricular outflow tract obstruction with intact ventricular septum, and detection of ventriculocoronary connections. *Heart* 1999;**81**:661-68.
- 5 **Kumar RK**, Newburger JW, Gauvreau K, *et al*. Comparison of outcome when hypoplastic left heart syndrome and transposition of the great arteries are diagnosed prenatally versus when diagnosis of these two conditions is made only postnatally. *Am J Cardiol* 1999;**83**:1649-53.
- 6 **Tworetzky W**, McElhinney DB, Reddy VM, *et al*. Improved surgical outcome after fetal diagnosis of hypoplastic left heart syndrome. *Circulation* 2001;**103**:1269-73.
- 7 **Mahle WT**, Clancy RR, McGaurn SP, *et al*. Impact of prenatal diagnosis on survival and early neurologic morbidity in neonates with hypoplastic left heart syndrome. *Pediatrics* 2001;**107**:1277-82.
- 8 **Franklin O**, Burch M, Manning N, *et al*. Prenatal diagnosis of coarctation of the aorta improves survival and reduces morbidity. *Heart* 2002;**87**:67-9.
- 9 **Bonnet D**, Coltri A, Butera G, *et al*. Detection of transposition of the great arteries in fetuses reduces neonatal morbidity and mortality. *Circulation* 1999;**99**:916-18.
- 10 **Bartlett JM**, Wypij D, Bellinger DC, *et al*. Effect of prenatal diagnosis on outcomes in D-transposition of the great arteries. *Pediatrics* 2004;**113**:335-40.
- 11 **Ewigman BG**, Crane JP, Frigoletto FD, *et al*. Effect of prenatal ultrasound screening on perinatal outcome. RADIUS Study group. *N Engl J Med* 1993;**329**:821-27.
- 12 **Leonard H**, Derrick G, O'Sullivan J, *et al*. Natural and unnatural history of pulmonary atresia. *Heart* 2000;**84**:499-503.
- 13 **Bull C**. Current and potential impact of fetal diagnosis on prevalence and spectrum of serious congenital heart disease at term in the UK. *Lancet* 1999;**354**:1242-47.
- 14 **Verheijen PM**, Lisowski LA, Stoutenbeek P, *et al*. Prenatal diagnosis of congenital heart disease affects preoperative acidosis in the newborn patient. *J Thorac Cardiovasc Surg* 2001;**121**:798-803.

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