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Prenatal diagnosis of critical congenital heart disease reduces risk of death from cardiovascular compromise prior to planned neonatal cardiac surgery: a meta-analysis

B. J. HOLLAND*, J. A. MYERS† and C. R. WOODS Jr†

**Division of Pediatric Cardiology, Department of Pediatrics, University of Louisville School of Medicine, Louisville, KY, USA; †Child and Adolescent Health Research and Design Support Unit, Department of Pediatrics, University of Louisville School of Medicine, Louisville, KY, USA*

KEYWORDS: congenital heart disease; fetal echocardiography; mortality; outcome; prenatal diagnosis

ABSTRACT

Objective *To determine if prenatal diagnosis improves the chance that a newborn with critical congenital heart disease will survive to undergo planned cardiac surgery.*

Methods *A systematic review of the medical literature identified eight studies which met the following criteria: compared outcomes between newborns with prenatal and those with postnatal diagnosis of critical congenital heart disease; compared groups of patients with the same anatomical diagnosis; provided detailed information on cardiac anatomy; included detailed information on preoperative cause of death. A meta-analysis was performed to assess differences in preoperative mortality rates between newborns with prenatal diagnosis and those with postnatal diagnosis. Patients with established risk factors for increased mortality (high risk) and those whose families chose comfort care rather than cardiac surgery were excluded.*

Results *In patients with comparable anatomy, standard risk, a parental desire to treat and optimal care, newborns with a prenatal diagnosis of critical congenital heart disease were significantly less likely to die prior to planned cardiac surgery than were those with a comparable postnatal diagnosis (pooled odds ratio, 0.26; 95% CI, 0.08–0.84).*

Conclusions *For newborns most likely to benefit from treatment for their critical congenital heart disease, because they did not have additional risk factors and their families pursued treatment, prenatal diagnosis reduced the risk of death prior to planned cardiac surgery relative to patients with a comparable postnatal diagnosis. Further study and efforts to improve prenatal diagnosis of congenital heart disease should therefore be considered.* *Copyright © 2015 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

At the heart of this analysis is a clinical question that has not been addressed adequately by previous studies in the literature: if two expectant mothers are each carrying a fetus with the same critical congenital heart disease, and one fetus has a prenatal diagnosis while the other does not, is one of the newborns more likely than the other to die after birth?

Most studies have focused on surgical and hospital outcomes, and have not shown improved survival following prenatal diagnosis of congenital heart disease[1–18]. However, the best assessment of the impact of prenatal diagnosis on outcome would consider overall newborn survival, including preoperative mortality. The preoperative course for a newborn with a postnatal diagnosis can be complicated if symptoms and cardiovascular compromise develop at home or in a community hospital prior to referral to a tertiary care center (Figure 1).

The Baltimore Washington Infant Study[19] and studies in the USA[20] and the UK[21] have shown that there are significant numbers of cases of congenital heart disease that go undetected and result in infant deaths, with diagnosis only postmortem. Existing studies have a number of limitations with respect to the assessment of preoperative mortality. There is a general selection bias in many, due to the exclusion of patients who died prior to cardiac surgery[1–4,6,7,11,15,18,22–24]. Others have

Correspondence to: Dr B. J. Holland, Division of Pediatric Cardiology, Department of Pediatrics, University of Louisville School of Medicine, Louisville, KY, USA (e-mail: brian.holland@louisville.edu)

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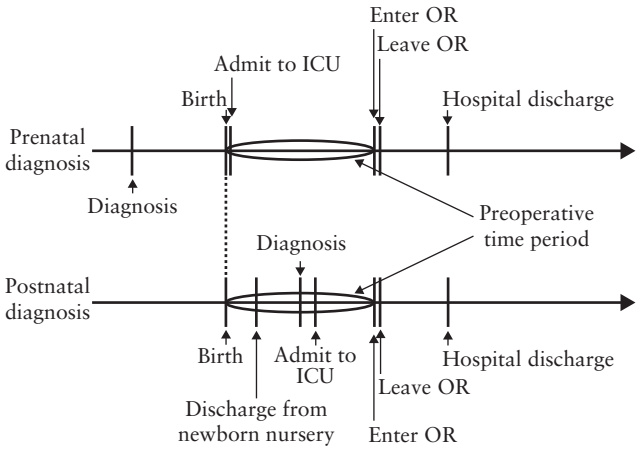

Figure 1 Parallel time lines for management of critical congenital heart disease diagnosed prenatally *vs* postnatally. ICU, intensive care unit; OR, operating room.

been limited by small numbers of preoperative deaths or heterogeneous patient populations with respect to anatomical diagnosis, the presence of known additional risk factors for mortality and the family's desire to pursue cardiac surgery[1,5,9,10,13,25–36]. Most studies to date have not allowed for accurate comparisons between groups due to a lack of detailed information on cardiac anatomy or preoperative cause of death[4,7,8,11,12,14,24,37–47].

In an attempt to overcome the limitations of individual studies in the literature, in this meta-analysis we focused on preoperative newborn survival, included only comparisons of groups of patients with the same anatomical diagnosis and combined the small numbers of patients from individual studies.

METHODS

The study design for this meta-analysis was based on the 2009 PRISMA Group statement[48]. The sections below follow the 2009 PRISMA checklist.

Protocol and registration

There is no review protocol or registration number for this meta-analysis.

Eligibility criteria (PICOS)

Participants: newborns with critical congenital heart disease. *Interventions*: prenatal diagnosis of critical congenital heart disease. *Comparisons*: detailed cardiac anatomy, presence of known additional risk factors for newborn mortality, parental desire to pursue cardiac surgery, detailed cause of death. *Outcomes*: preoperative mortality. *Study design*: meta-analysis.

The eight studies analyzed were all original single-center retrospective reviews of patients with critical congenital heart disease which compared outcomes of patients who were diagnosed prenatally with those of patients who were diagnosed after birth.

Information sources, search and study selection

To identify articles, registries and conference abstracts for inclusion in the meta-analysis, Internet searches of MEDLINE via PubMed, EMBASE and the International Clinical Trials Registry Platform were performed. This included English-language publications from 1990 to 2015 (no information comparing prenatal and postnatal diagnosis groups with critical congenital heart disease was found prior to 1990). The date of the last search was 10 March 2015. Records were screened in four stages, as outlined in Figure 2, and eight articles were identified for inclusion in the meta-analysis. All patients in these studies either died or underwent cardiac surgery in the newborn period.

Data collection process

An independent analysis of data provided in the original published articles, including data, when details were available, on patients excluded from previous analysis, was performed by the faculty of the University of Louisville School of Medicine, Louisville, KY, USA.

Data items

The data items analyzed were: prenatal diagnosis of congenital heart disease, postnatal diagnosis of congenital heart disease, cardiac anatomical diagnosis, death prior to planned cardiac surgery, survival to cardiac surgery, parental decision not to pursue cardiac surgery, presence of known risk factors associated with increased newborn mortality[49] (associated major extracardiac, genetic or chromosomal malformations, low birth weight < 2.5 kg, prematurity ≤ 35 weeks' gestation, severe neonatal infection or meconium aspiration, hypoplastic left heart syndrome (HLHS) with intact or highly restrictive atrial septum, complex cardiac anatomy not amenable to neonatal surgical palliation) and cause of death. The eight studies analyzed each contained newborns with comparable anatomy in the prenatal-diagnosis and postnatal-diagnosis groups. Diagnoses included HLHS[2,6], d-transposition of the great arteries (D-TGA)[2,50,51], coarctation of the aorta[52], pulmonary atresia[53], truncus arteriosus[54] and critical left heart obstruction with ductal-dependent circulation[3], which included coarctation of the aorta, aortic stenosis, subaortic stenosis and HLHS (Table 1).

Statistical analysis, risk of bias, summary measures, synthesis of results and additional analyses

The primary outcome was preoperative death rate. The metrics used were pooled proportion of preoperative death and pooled odds ratio (OR) for preoperative death, obtained from the meta-analysis. The software used was Comprehensive Meta Analysis, version 2 (Biostat, Englewood, NJ, USA). Results for the eight studies included were combined statistically in a meta-analysis

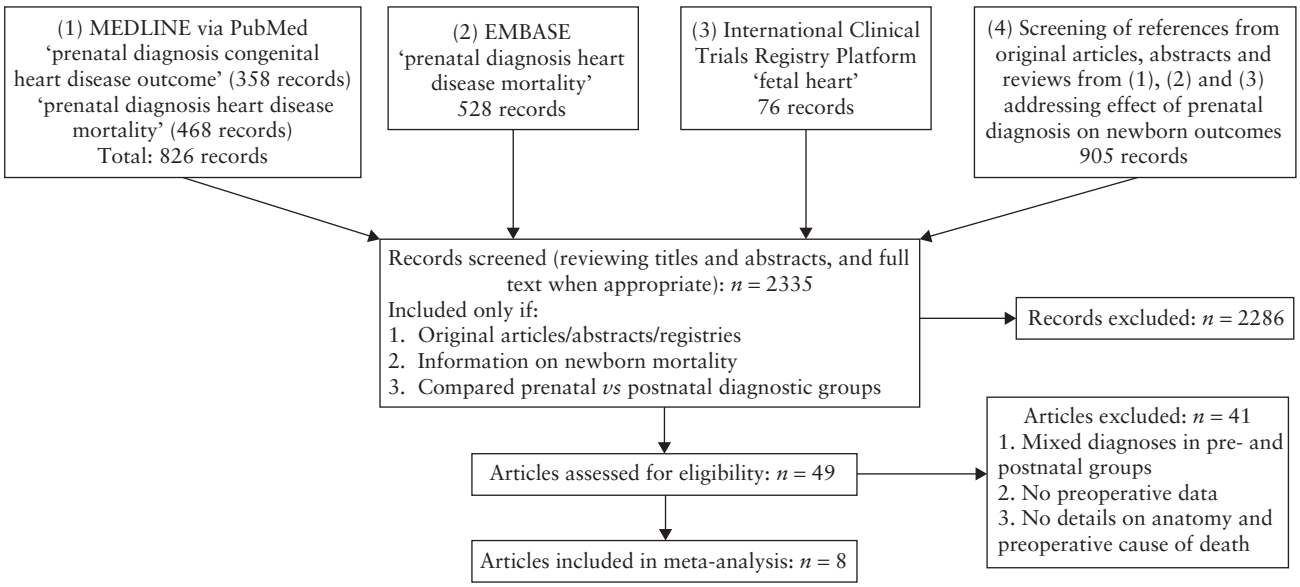

Figure 2 Information sources and search parameters for selection of studies in this meta-analysis

Table 1 Studies included in this meta-analysis of patients with critical congenital heart disease

Study	*Cardiac diagnosis*	*Patients* (n)
Kumar (1999)[2]*	HLHS	217
Kumar (1999)[2]*	D-TGA	422
Eapen (1998)[3]	Critical left heart obstruction	63
Kipps (2011)[6]	HLHS	87
Bonnet (1999)[50]	D-TGA	261
Franklin (2002)[52]	Coarctation of the aorta	32
Tzifa (2007)[53]	Pulmonary atresia	58
Swanson (2009)[54]	Truncus arteriosus	112
Raboisson (2009)[51]	D-TGA	121
Total		1373

Only first author of each study is given. *Study by Kumar *et al.* included separate analyses for patients with hypoplastic left heart syndrome (HLHS) and d-transposition of the great arteries (D-TGA).

to generate an overall pooled summary statistic with a 95% confidence interval. Similarly, meta-analysis techniques using pooled mortality rates were used to assess differences in stratified mortality rates between newborns with a prenatal versus postnatal diagnosis of critical congenital heart disease. A random-effects model meta-analysis was used if there was heterogeneity between the studies, heterogeneity being defined by $P < 0.1$ or I^2 index $> 50\%$. The I^2 index was calculated as $100 \times ((\text{Cochran's Q-df})/\text{Cochran's Q})$. Egger's test with a significance level of 0.05 was used to evaluate the publication bias. In addition, since Egger's test may perform poorly for dichotomous data, publication bias was also estimated using the Harbord test. The risk of bias of cohort and case–control studies was assessed using the Newcastle-Ottawa Scale (NOS); this assessed three domains: selection of study groups, comparability of study groups and ascertainment of outcomes. When zero events were reported, a continuity correction was applied to the relevant contingency tables used in the meta-analysis.

RESULTS

The eight studies included in total 1373 patients, 297 (22%) with a prenatal diagnosis and 1076 (78%) patients with a postnatal diagnosis of critical congenital heart disease.

Analysis of all patients, all levels of risk and all levels of care (eight studies[2,3,6,50–54])

Death occurred in the preoperative time period in 30/297 (10.1%) cases with a prenatal diagnosis, and in 60/1076 (5.6%) cases with a postnatal diagnosis. The odds of a patient with a prenatal diagnosis dying was nearly twice that of a patient with a postnatal diagnosis (pooled OR = 1.90; 95% CI, 1.20–3.01). Examination of the pooled data shows that patients with a prenatal diagnosis were more likely to be high risk ($n = 17$, 5.7% *vs* $n = 13$, 1.2%) and more likely to choose comfort care ($n = 11$, 3.7% *vs* $n = 16$, 1.5%).

Exclusion of high-risk and comfort-care patients

High-risk patients and those undergoing comfort care were excluded from further analysis; all of these cases died in the neonatal period. Of the 297 patients with a prenatal diagnosis, 11 (3.7%) patients died following a parental decision not to pursue cardiac surgery ('comfort care'), 17 (5.7%) patients died and had known additional risk factors for newborn mortality, as described above under 'data items' in the Methods section ('high risk') (Table 2). The remaining 269 (90.6%) patients did not have known additional risk factors and the parents did not opt for comfort care ('standard risk, planned cardiac surgery').

Of the 1076 patients with a postnatal diagnosis, 16 (1.5%) patients died following a parental decision not to pursue cardiac surgery ('comfort care'), 13 (1.2%)

Table 2 Details of patients with critical congenital heart disease excluded from further analysis because they were high risk

Time of diagnosis	n	*Risk factor*	*Study*
Postnatal	1	Associated major congenital malformation	Kumar (1999)[2]
Postnatal	3	Prematurity and lung disease	Kumar (1999)[2]
Postnatal	3	Complex cardiac anatomy	Kumar (1999)[2]
Postnatal	1	HLHS with highly restrictive atrial septum	Kumar (1999)[2]
Postnatal	1	Prematurity	Kumar (1999)[2]
Postnatal	1	Meconium aspiration	Kumar (1999)[2]
Postnatal	1	HLHS with total anomalous pulmonary venous return	Eapen (1998)[3]
Postnatal	2	HLHS with intact or highly restrictive atrial septum	Kipps (2011)[6]
Total	13		
Prenatal	2	Associated major congenital malformation	Kumar (1999)[2]
Prenatal	2	Prematurity and lung disease	Kumar (1999)[2]
Prenatal	2	HLHS with restrictive atrial septum	Kumar (1999)[2]
Prenatal	1	Severe congenital CMV infection	Eapen (1998)[3]
Prenatal	4	HLHS with intact or highly restrictive atrial septum	Kipps (2011)[6]
Prenatal	6	Prematurity and/or major congenital malformation	Swanson (2009)[54]
Total	17		

Only first author of each study is given. CMV, cytomegalovirus; HLHS, hypoplastic left heart syndrome.

patients died and had known additional risk factors for newborn mortality ('high risk') (Table 2). The remaining 1047 (97.3%) patients did not have known additional risk factors and the parents did not opt for comfort care ('standard risk, planned cardiac surgery').

Analysis of patients with standard risk and planned cardiac surgery (eight studies[2,3,6,50–54])

Of the 1316 cases with standard risk (i.e. no additional risk for newborn mortality; see 'data items' in Methods) and planned cardiac surgery, preoperative death occurred in 2/269 (0.7%) cases with a prenatal diagnosis, and in 31/1047 (3.0%) cases with a postnatal diagnosis (Figure 3 and Table 3). It was assumed that patients with D-TGA or coarctation of the aorta which were first diagnosed at autopsy would have pursued cardiac surgery had they known the diagnosis.

An 'intention-to-treat' meta-analysis was performed using the random-effects model on all patients with standard risk and planned cardiac surgery in all eight studies[2,3,6,50–54]. This meta-analysis did not indicate a statistically significant difference in preoperative mortality between patients with a prenatal diagnosis and those with a postnatal diagnosis (pooled OR = 0.36; 95% CI, 0.12–1.12) (Figure 4). One study[54] was not included in the forest plot because none of the patients died preoperatively in either of the groups, resulting in an undefined OR which might distort the figure; however, the data from this study were used in the meta-analysis for calculating the pooled OR. Not all of the patients in the prenatal diagnosis group received optimal care: one patient with a prenatal diagnosis of D-TGA was not delivered at or near a cardiac center capable of performing a balloon atrial septostomy[51]. This patient was delivered at an outlying hospital, developed cyanosis, acidosis and multiorgan failure, and was transferred to a cardiac center intensive care unit at the age of 3 hours. Balloon atrial septostomy was performed at that time but failed to restore normal hemodynamic conditions, and the infant died prior to attempted cardiac surgery.

Analysis of patients with standard risk, planned cardiac surgery and optimal care (seven studies[2,3,6,50,52–54])

An 'optimal care' meta-analysis using the random-effects model was performed on all patients with standard risk, planned cardiac surgery and optimal care. Optimal care was defined as delivery of newborns with a prenatal diagnosis of critical congenital heart disease at or near a hospital with specialized newborn cardiac care including balloon atrial septostomy. The study with the single patient described above who did not receive optimal care[51] was excluded from this analysis. Preoperative death occurred in 1/221 (0.5%) cases with a prenatal diagnosis and in 31/974 (3.2%) cases with a postnatal diagnosis. Meta-analysis indicated that prenatal diagnosis was associated with significantly less preoperative mortality for standard-risk patients with planned cardiac surgery receiving optimal care (pooled OR = 0.25; 95% CI, 0.08–0.84) (Figure 5). The study[54] with no preoperative deaths in either group was also excluded from this forest plot, though its data were used in the calculation of pooled OR.

Analysis of heterogeneity and publication bias

No heterogeneity was observed in the meta-analysis ($I^2 = 0.0\%$, $P = 0.859$) and there was no evidence of publication bias in the eight studies included. The Egger's and Harbord test results were insignificant, suggesting no individual study had excessive influence on the pooled effect. The NOS scores suggested low risk of bias (all studies scored ≥ 6).

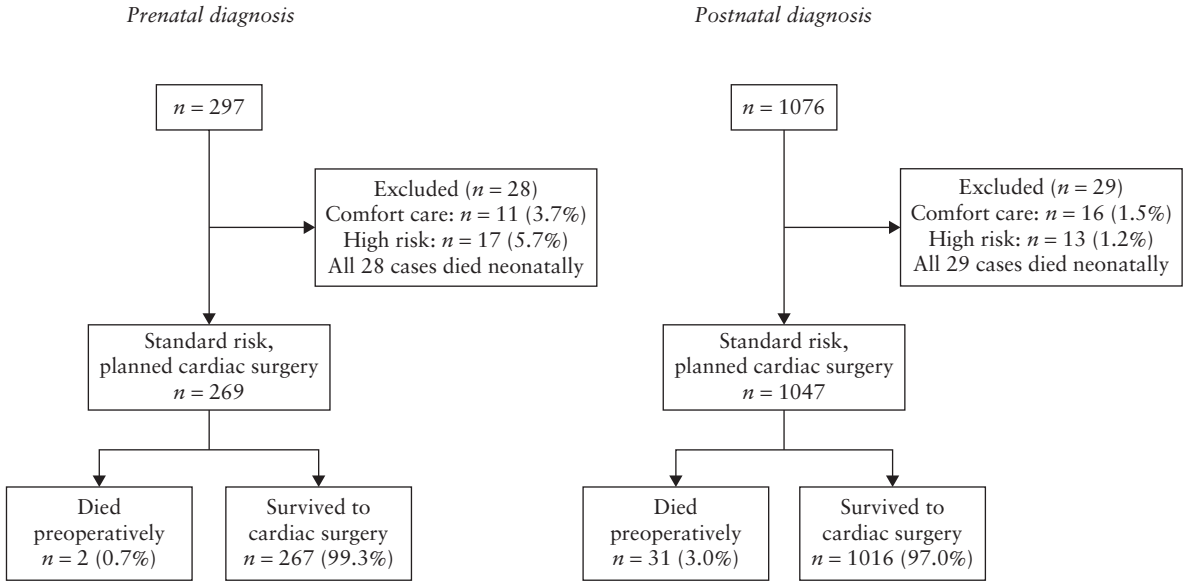

Figure 3 Summary of outcomes of patients with critical congenital heart disease diagnosed prenatally or postnatally.

Table 3 Details of patients with critical congenital heart disease, with standard risk and planned cardiac surgery, who died prior to surgery

Time of diagnosis	n	*Cardiac diagnosis and cause of death*	*Study*
Postnatal	4	HLHS, incomplete recovery from metabolic insult	Kumar (1999)[2]
Postnatal	2	D-TGA, restrictive atrial septum, hypoxemia, acidosis	Kumar (1999)[2]
Postnatal	3	Critical left heart obstruction, multi-organ system failure	Eapen (1998)[3]
Postnatal	1	Critical left heart obstruction, died before surgery	Eapen (1998)[3]
Postnatal	2	HLHS, severe end-organ dysfunction	Kipps (2011)[6]
Postnatal	8	D-TGA, diagnosis made at autopsy*	Bonnet (1999)[50]
Postnatal	7	D-TGA, multiorgan failure	Bonnet (1999)[50]
Postnatal	3	Coarctation of the aorta, diagnosis made at autopsy*	Franklin (2002)[52]
Postnatal	1	Pulmonary atresia/IVS, myocardial failure	Tzifa (2007)[53]
Total	31		
Prenatal	1	Pulmonary atresia/IVS, necrotizing enterocolitis awaiting surgery	Tzifa (2007)[53]
Prenatal	1	D-TGA, acidosis, multiorgan failure, bleeding†	Raboisson (2009)[51]
Total	2		

Only first author of each study is given. *For d-transposition of the great arteries (D-TGA) and coarctation of the aorta found at autopsy, planned cardiac surgery was assumed if diagnosis had been made prior to death. †Despite prenatal diagnosis, delivered at an outlying hospital, transferred to intensive care unit at age of 3 hours with major cyanosis, multiorgan failure and acidosis; balloon atrial septostomy performed at that time, but failed to restore normal hemodynamic conditions. HLHS, hypoplastic left heart syndrome; IVS, interventricular septum.

DISCUSSION

This analysis shows that prenatal diagnosis of critical congenital heart disease improves newborn preoperative survival. Newborns with a postnatal diagnosis were more likely to die of cardiovascular compromise prior to planned cardiac surgery than were those with a prenatal diagnosis.

Although previous studies which focused on operative and postoperative outcomes have not shown a survival benefit for patients with a prenatal diagnosis[1–18,22–47], these studies do not fully address the practical clinical question posed in the Introduction. If two expectant mothers are both carrying fetuses with the same critical congenital heart disease, one diagnosed prenatally and the other postnatally, the surgical-outcome studies show that, if both of these newborns first survive to undergo cardiac surgery, then they both have the same chance to survive after surgery. This was hinted at in the discussion section of one of the analyzed studies, which stated, 'It is important to note that several of the most critical infants in the postnatal group were considered too high risk and never underwent surgery'[3]. Thus, presurgical clinical decisions not to pursue surgery may have influenced outcomes.

The results of this analysis not only show that prenatal diagnosis improves preoperative newborn survival, but also suggest that a prenatal diagnosis may therefore improve overall newborn survival. In this meta-analysis, newborns with standard risk and a prenatal diagnosis had improved chances of surviving to undergo planned cardiac surgery compared with those diagnosed postnatally, provided they followed an optimal delivery plan. Based on previous studies in the literature[1–18,22–47], they would

Study	Statistics: Odds ratio	Lower limit	Upper limit	Z-value	P-value	Deaths/Total: Prenatal	Postnatal
Kumar (1992)[2]	0.881	0.049	15.882	–0.086	0.932	0/46	6/538
Eapen (1998)[3]	0.226	0.011	4.516	–0.973	0.331	0/13	4/31
Bonnet (1990)[50]	0.098	0.006	1.662	–1.608	0.108	0/57	15/189
Franklin (2002)[52]	0.224	0.010	4.800	–0.956	0.339	0/10	3/19
Kipps (2011)[6]	0.099	0.005	2.148	–1.473	0.141	0/45	2/24
Raboisson (2009)[51]	4.742	0.189	118.873	0.947	0.344	1/47	0/73
Tzifa (2007)[53]	0.543	0.032	9.176	–0.423	0.672	1/36	1/20
Pooled analysis	0.363	0.118	1.118	–1.766	0.077		

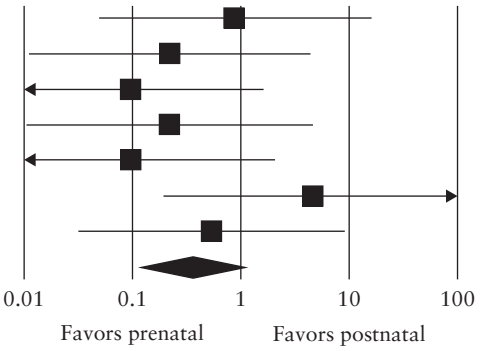

Figure 4 Meta-analysis of critical congenital heart disease patients with standard risk, planned cardiac surgery and intention-to-treat: forest plot of preoperative death for patients with prenatal *vs* postnatal diagnosis. *One study (Swanson *et al.*[54]) was not included in the forest plot because none of the patients died preoperatively in either of the groups, resulting in an undefined odds ratio which might distort the figure; however, the data from this study were used in the meta-analysis for calculating the pooled odds ratio.

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Tzifa (2007)[53]	0.543	0.032	9.176	–0.423	0.672	1/36	1/20
Pooled analysis	0.254	0.076	0.843	–2.238	0.025		

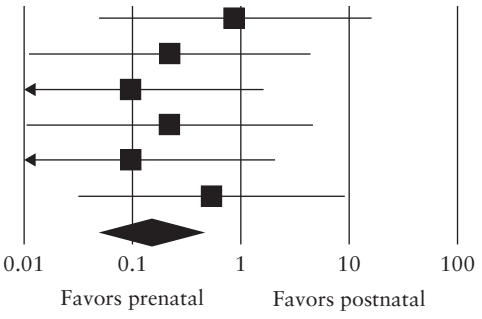

Figure 5 Meta-analysis of critical congenital heart disease patients with standard risk, planned cardiac surgery and optimal care: forest plot of preoperative death for patients with prenatal *vs* postnatal diagnosis. *One study (Swanson *et al.*[54]) was not included in the forest plot because none of the patients died preoperatively in either of the groups, resulting in an undefined odds ratio which might distort the figure; however, the data from this study were used in the meta-analysis for calculating the pooled odds ratio.

then have had the same chance of surviving after cardiac surgery as had those with a postnatal diagnosis who had also survived to undergo surgery.

The implications of an improvement in overall newborn survival following prenatal diagnosis could be far-reaching; they support expanded efforts to improve prenatal screening for congenital heart disease during routine obstetric examination, changes in sonographer training, updated recommendations for ultrasound examinations and improved access to fetal echocardiograms. Each of these involves significant time and resources and changes in practice for providers who care for women during pregnancy.

Consideration should be given to the inclusion of all outcomes when designing future studies looking at the impact of prenatal diagnosis on critical congenital heart disease. Ideally, such studies would include terminations of pregnancy, patients diagnosed at autopsy and every patient who presents to the hospital with critical congenital heart disease, not just those who undergo cardiac surgery. The small numbers of deaths in each of the individual studies included in this meta-analysis suggest that a future multicenter collaboration may provide the most useful information.

There are some limitations to consider. The survival benefit from prenatal diagnosis on the population as a whole may actually be greater than was seen in this meta-analysis. Six of the eight analyzed studies[2,3,6,51,53,54] did not include patients diagnosed at autopsy and one of the studies[50] had a formal exclusion for patients referred to the surgical center from afar. Inclusion of patients who die before admission to hospital and those who are referred from a distance could further strengthen the

argument for improved preoperative survival following prenatal diagnosis.

This analysis did not show a decrease in all-cause mortality following prenatal diagnosis of critical congenital heart disease. However, as has been shown previously[9,10], there were more high-risk and comfort-care patients in the prenatal compared with the postnatal diagnosis group. To assess better the impact of prenatal diagnosis on newborn preoperative mortality and eliminate the confounding effect of other causes of newborn mortality, high-risk and comfort-care patients were excluded from further analysis.

The intention-to-treat analysis did not show a statistically significant decrease in newborn mortality following prenatal diagnosis. This part of the analysis was affected strongly by the preoperative death of a single patient who did not receive optimal newborn care. While failure to follow the optimal postnatal pathway is an important practical consideration in fetal medicine, the impact of a prenatal diagnosis is based on the ability to have optimal care available to prevent cardiovascular compromise immediately after birth. This patient had a prenatal diagnosis, but the treatment available at birth was no different from that available to patients with a postnatal diagnosis. A separate analysis to assess the impact of prenatal diagnosis on patients who had optimal care available at birth, performed without the study which included this single patient, showed a statistically significant decrease in newborn preoperative mortality following prenatal diagnosis. The statistical effect of one patient without optimal prenatal care seems to support the proposal for a future multicenter study with larger numbers of patients and sufficient statistical power.

Many of these studies were done prior to the American Heart Association's scientific statement on newborn pulse oximetry screening for the detection of congenital heart disease[55]. It is possible that newborns with congenital heart disease who undergo pulse oximetry screening in the future may be detected earlier than were the patients in these analyzed studies. However, pulse oximetry screening is not yet available universally and is not performed until 24 hours post delivery, which may be too late to prevent neonatal cardiovascular compromise in some infants. Pulse oximetry is only approximately 70% sensitive overall[55], and has very low sensitivity for coarctation of the aorta and critical aortic stenosis, which may result in demise of newborns who are discharged home without a diagnosis.

This analysis included only patients with the most critical congenital heart disease, requiring newborn surgery or intervention. Therefore, the survival benefit seen here may not necessarily apply to newborns who have a prenatal diagnosis of other congenital heart defects, such as atrioventricular canal or tetralogy of Fallot. Prenatal diagnosis of critical congenital heart disease can have other significant impacts on outcome which are not addressed in this analysis, such as rates of termination of pregnancy[56–58].

The studies analyzed were all retrospective reviews, not designed specifically to look at preoperative mortality, with the inherent possibility of incomplete or inaccurate data or incorrect classification of information. An attempt was made to minimize this by carefully screening articles and analyzing only those with complete, detailed information, and by clearly defining variables and parameters used in this analysis.

In conclusion, having shown that prenatal diagnosis of critical congenital heart disease improves newborn preoperative survival, we believe that further study and efforts to improve prenatal diagnosis of congenital heart disease should be considered.

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This article has been selected for Journal Club.

A slide presentation, prepared by Dr Maddalena Morlando, one of UOG's Editors for Trainees, is available online.

Chinese translation by Dr Yang Fang. Spanish translation by Dr Masami Yamamoto.

