Efficacy of prenatal diagnosis of major congenital heart disease on perinatal management and perioperative mortality: a meta-analysis

Yi-Fei Li, Kai-Yu Zhou, Jie Fang, Chuan Wang, Yi-Min Hua, De-Zhi Mu
Chengdu, China

Background: **There is no consensus on the effectiveness of prenatal diagnosis except for hospitalized outcomes. Hence, a meta-analysis of published literature was conducted to assess the effect of prenatal diagnosis.**

Methods: **Literature review has identified relevant studies up to December 2013. A meta-analysis was performed according to the guidelines from the Cochrane review group and the PRISMA statement. Studies were identified by searching PubMed, Embase, the Cochrane Central Register of Controlled Trials and World Health Orgnization clinical trials registry center. Meta-analysis was performed in a fixed/random-effect model using Revman 5.1.1 according to the guidelines from the Cochrane review group and the PRISMA guidelines.**

Results: **The results from 13 cohort studies in 12 articles were analyzed to determine the optimal treatment with the lower rate of perioperative mortality in prenatal diagnosis. The superiority of a prenatal diagnosis has been proven because the surgical procedure could be done in the early neonatal period (95%CI, -0.76, -0.40). The prenatal diagnosis has also remarkably reduced the preoperative and postoperative mortality rates in cases of transposition of the great arteries (95%CI=0.06, 0.80; 95%CI=0.01, 0.82, respectively), as well as the overall results with all subtypes (95%CI=0.18, 0.94; 95%CI=0.46, 0.94, respectively).**

Conclusions: **Prenatal diagnosis is effective in perinatal management with an earlier intervention for major congenital heart disease, but only results in a reduced perioperative mortality in cases of transposition of the great arteries. Further investigations are required to evaluate the effect of prenatal diagnosis on life quality during a long-term follow-up.**

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Key words: **congenital heart disease;**
delivery;
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meta-analysis

Introduction

Congenital heart disease (CHD) is the most common birth defect, with an incidence of 6‰-8‰ in all live births.[1] Major CHD is a kind of cardiac abnormalities which will have a significant effect on the life of a child,[2] and most of them require a surgical procedure in their early life.[3] In recent years, fetal echocardiography has become a widespread tool for prenatal diagnosis of CHD.[4] The majority of cases of CHD, especially major ones, such as hypoplastic left heart syndrome (HLHS) and transposition of the great arteries (TGA), single ventricle (SV), tetralogy of Fallot (TOF) and double outlet right ventricle (DORV) can be identified prenatally with high accuracy in collaboration with more than 3 scanning sections.[5] Moreover, prenatal diagnosis allows for optimal perinatal and perioperative management, such as delivery in a high-risk tertiary center, immediate mechanical ventilation and balloon atrioseptostomy or prostaglandin administration in ductus-dependent CHD, if necessary.[6,7]

Patients with major CHD may suffer from neurological impairment by exposure to harmful hemodynamics which is also related to the death of children for complex factors.[8] It has been hypothesized that such risk-adapted

Author Affiliations: Department of Pediatrics, Ministry of Education Key Laboratory of Women and Children's Diseases and Birth Defects (Li YF, Zhou KY, Wang C, Hua YM, Mu DZ), Program for Yangtze River Scholars and Innovative Research Team in University, West China Second University Hospital, Sichuan University, Chengdu, China (Zhou KY, Hua YM, Mu DZ); West China Medical School (Li YF, Wang C), West China Stomatology School, Sichuan University, Chengdu, China (Fang J)

Corresponding Author: De-Zhi Mu, Department of Pediatrics, West China Second University Hospital, Sichuan University, No. 20, 3rd section, South Renmin Road, Chengdu 610041, China (Tel: +86-28-85501352; Fax: +86-28-85501059; Email: dezhi.mu@ucsf.edu)

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management which benefits from prenatal diagnosis would improve the outcomes of affected newborns by reducing hypoxemic complications and stabilizing the clinical condition before surgery with appropriate management, but this has not reached a general agreement. Therefore, this meta-analysis is to analyze the effect of prenatal diagnosis on the delivery variables, preoperative management and perioperative mortality in patients with major CHD. Thus, based on this meta-analysis, perinatal administrations and perioperative outcomes have been analyzed to demonstrate whether prenatal diagnosis could alter their perinatal managements and improve the prognosis of major CHD between prenatally and postnatally diagnosed cases.

Methods

Data sources

PubMed, Ovid Embase, the Cochrane Central Register of Controlled Trials, and the World Health Organization clinical trials registry were searched. The search strategy was "diagnosis AND (heart defects, congenital [MeSH terms] OR congenital heart disease OR CHD) AND (prenatal OR antenatal OR intrauterine OR in utero) AND (postnatal OR neonatal) AND (outcome OR prognosis)." The search was updated through December 2013.

Study selection

The citations initially selected by the search were first retrieved as title and/or abstract and preliminarily screened. Potentially relevant reports were then obtained as complete manuscripts and assessed for compliance to the inclusion and exclusion criteria.

The inclusion criteria were as follows: 1) the patients were identified to have CHD by fetal echocardiography and/or other diagnosis methods; and 2) the report represented a cohort study; 3) evaluation was performed between prenatally and postnatally diagnosed groups; 4) the report contained at least one of the following outcomes: delivery variables, preoperative management and mortality; 5) all patients suffered from major CHD; and 6) the subtypes of CHD enrolled were limited or showed no significant difference in subtypes' mixture.

The exclusion criteria were as follows: 1) the same cohort had been studied in another study; 2) the same subtypes of CHD underwent different procedures.

Data collection and quality assessment

Two investigators (Li YF, Zhou KY) independently assessed the eligibility of reports at the title and/or abstract level, and another investigator (Mu DZ) determined the divergences; studies that met the inclusion criteria were selected for further analysis. A quality assessment was made independently by the two investigators according to the quality assessment guidelines of the non-randomized controlled intervention study by Deeks et al.[9]

Outcome measures of perinatal mortality and perioperative mortality

The measured delivery variables were gestation age, birth weight and Apgar score at 1 and 5 minutes postpartum. Perinatal managements included intubation at birth, prostaglandin administration before operation and the age of infants undergoing operation. The most important aspect in evaluating the prenatal diagnosis and postnatal diagnosis effects on the prognosis was the preoperative mortality and postoperative hospital mortality. Postoperative hospital mortality referred to neonatal deaths during the hospitalization after surgical procedure both related to surgical and non-surgical factors.

Assessment of heterogeneity

Q test was conducted on the research effect size to evaluate heterogeneity. If the results were not heterogeneous (I^2<50%), count data were analyzed using a fixed effect model (Peto's method). If heterogeneity was detected (I^2≥50%), the random effect model was used. Meta-regression was performed to identify whether subtypes of major CHD was a potential factor related to high heterogeneity by STATA 11.0 (Stata Corporation, College Station, Texas, USA).

Analysis of publication bias

Begg's funnel plot was presented for possible publication bias. Asymmetric plot indicated existence of publication bias. Additionally, we measured the funnel plot asymmetry using Egger's test. P<0.05 was considered statistically significant. Publication bias analysis was performed using STATA 11.0.

Data synthesis

This systematic review was performed according to the PRISMA guidelines. Pooled analyses of selected studies were performed with Revman 5.1.1. Pooled odds ratio and 95% confidence interval (CI) were presented. Continuous data were analyzed with weighted standard mean difference (SMD) and 95%CI as large mean difference variables. All the continuous variables were calculated as mean±standard deviation (SD). In the evaluation of perioperative mortality, subgroups analyses were conducted according to subtypes of major CHD. The sensitivity analysis was conducted in evaluations which included more than 5 studies.

Results

Study evaluation

A total of 839 citations were retrieved. After reading the titles and abstracts, 814 citations were excluded according to the selection criteria. After a manual retrospective search of the related publications, three articles[10-12] were added to the group of considered articles and 28 studies were identified finally. Among them, 16 studies were excluded after reading the completed articles, including eight studies that compared the subtypes of the prenatal and postnatal diagnosed patients, five studies that enrolled patients with significantly different subtypes and 3 studies focusing on proving the accuracy of ultrasounds in detecting CHD prenatally. Ultimately, 13 cohort studies in 12 articles[10-21] were selected for meta-analysis comparison between prenatal and postnatal diagnoses (Fig. 1). Particularly, one article contained two studies with such comparison: one related to HLHS and another related to TGA.[19] In 1618 patients included, 469 patients were diagnosed with major CHD prenatally, and 1149 patients with major CHD after birth. All the patients were free from extra-cardiac abnormalities, chromosomal abnormalities and genetic syndromes. The quality of all the articles was acceptable. Table 1 shows the basic characteristics of included studies and the quality evaluation of these studies. All of the studies were qualified according to the inclusion criteria.

Publication bias

To assess the publication bias of the included studies, Begg's funnel plot was constructed and Egger's test was performed. The funnel plot was symmetrical, and indicated the absence of publication bias (Fig. 2A and B). Furthermore, the Egger's test provided quantitative evidence for the lack of publication bias (t=-1.21, P=0.282).

Meta-regression of major CHD subtypes

As the subtypes of major CHD might be important for the advantage evaluation from prenatal diagnosis, a meta-regression had been done to identify whether major CHD subtype was a factor to generate this heterogeneity. The result from the meta-regression showed that subtypes of CHD made no contribution to the high heterogeneity (standard error=0.18, 95%CI, -0.44, 0.54, P=0.805) (Fig. 2C).

Gestation week at delivery

For gestation week evaluation, 1171 patients from the 8 studies were enrolled.[10,12-15,17,18,21] There were significant differences in gestation weeks between the two groups (SMD=-0.34, 95%CI, -0.47, -0.21, P<0.00001). There was no heterogeneity across the studies (I^2=22%), and the results were analyzed according to a fixed effect

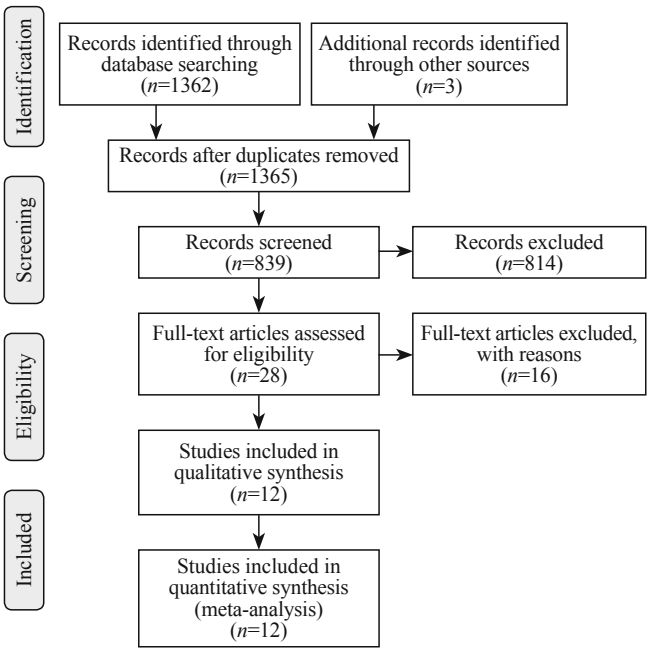

Fig. 1. Flow chart of study selection process.

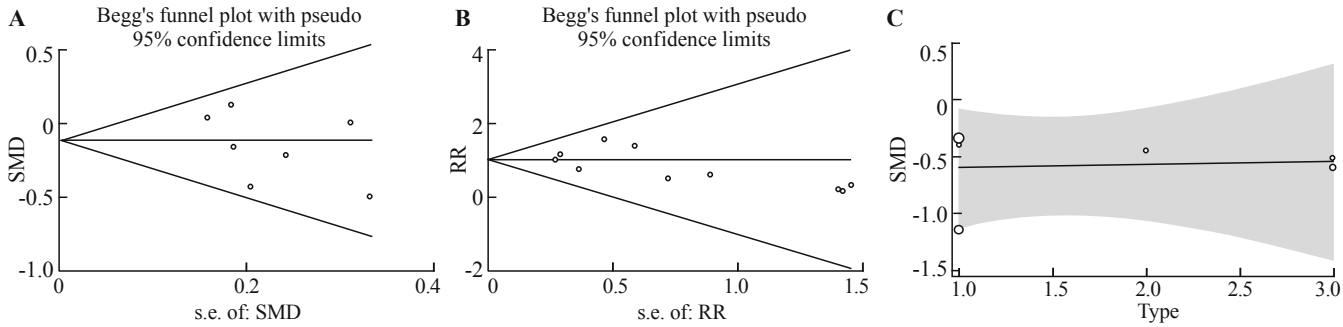

Fig. 2. A&B: Begg's funnel plot for publication bias test on included studies of perinatal managements and perioperative mortalities, respectively. **C**: Meta-regression showed that congenital heart disease types made no contribution to the heterogeneity (standard error=0.18, 95% CI, -0.44, 0.54, P=0.805). Description: the funnel plot seemed symmetrical, indicating the absence of publication bias. SMD: standard mean difference; RR: relative risk.

Table 1. Main characteristics of included studies

Author	Year	Regions of patients	No. subjects	Study cohort	Procedure of surgery	Follow-up time	Main indication for prognosis	Treatment *in utero*	Any attempt to balance groups by design	Identification of prognosis factors	Case-mixed adjustment
Lagopoulos	2010	Canada	121 (Prenatal *n*=69 *vs.* Postnatal *n*=52)	Double outlets right ventricle	Anatomic repairs+ univentrical repair	6 y	Survival rate	No	All the included cases are from the same research center, with good homogeneity	Reported the gestation age, weight, administration, surgical procedure, and subtypes characteristics, etc.	Yes
Wan	2009	Canada+ USA	53 (Prenatal *n*=14 *vs.* Postnatal *n*=39)	C-transposition of the great arteries	Double switch repair+anatomic repairs	Median 23 mon (range 0.7 to 68)	Survival rate	No	All the included cases are within the same strategy	Reported the gestation age, weight, gender, administration, surgical procedure, and subtypes characteristics, etc.	Yes
Raboisson	2009	France	121 (Prenatal *n*=48 *vs.* Postnatal *n*=73)	Transposition of the great arteries	Arterial switch operatio+balloon atrioseptotomy	Hospital stay after operation	Intensive unit varies	No	All the included cases are from the same research center, with good homogeneity	Reported the gestation age, weight, surgical procedure and delivery room variables, etc.	None
Glatz	2007	USA	38 (Prenatal *n*=26 *vs.* Postnatal *n*=12)	Hypoplastic left heart syndrome	Norwood procedure	3 y	Survival rate	Yes[§]	All the included cases are from the same research center, with good homogeneity	Reported the gestation age, weight, genetic syndromes, hospital course, surgical procedure and subtypes characteristics, etc.	Yes
Fuchs[†]	2007	Germany	257 (Prenatal *n*=49 *vs.* Postnatal *n*=208)	Mixed types without differences between groups	Not mentioned	Up to 130 mon (median 37.3)	Survival rate	No	All the included cases are from the same research center, with good homogeneity	Reported the gestation age, weight, gender, delivery room variables and subtypes characteristics, etc.	None
Franklin	2002	UK	32 (Prenatal *n*=10 *vs.* Postnatal *n*=22)	Transposition of the great arteries	Arterial switch operatio+ balloon atrioseptotomy	Hospital stay after operation	Operative mortality	No	All the included cases are from the same research center, with good homogeneity	Reported the delivery room variables, surgical procedure and subtypes characteristics, etc.	None
Verheijen	2001	Netherland	65 (Prenatal *n*=39 *vs.* Postnatal *n*=26)	Mixed types without differences between groups	Not mentioned	1 mon[‡]	Operative mortality	No	All the included cases are within the same strategy	Reported the gestation age, weight, gender, delivery room variables and subtypes characteristics, etc.	Yes
Tworetzky	2001	USA	88 (Prenatal *n*=14 *vs.* Postnatal *n*=38)	Hypoplastic left heart syndrome	Norwood procedure	Hospital stay after operation	Operative mortality	No	All the included cases are from the same research center, with good homogeneity	Reported the gestation age, weight, gender, surgical procedure and subtypes characteristics, etc.	None
Kumar[*]	1999	USA	HLHS: 74 (Prenatal *n*=27 *vs.* Postnatal *n*=47) D-TGA: 42 (Prenatal *n*=14 *vs.* Postnatal *n*=28)	Hypoplastic left heart syndrome+ D-transposition of the great arteries	Norwood procedure+ arterial switch operation	Hospital stay after operation	Operative mortality	No	All the included cases are from the same research center, with good homogeneity	Reported the gestation age, weight, gender, delivery room variables, surgical procedure and subtypes characteristics, etc.	None
Bonnet	1999	France	261 (Prenatal *n*=57 *vs.* Postnatal *n*=204)	Transposition of the great arteries	Not mentioned	Hospital stay after operation	Operative mortality	No	All the included cases are from the same research center, with good homogeneity	Reported the gestation age, weight, gender, administration and subtypes characteristics, etc.	None
Eapen	1998	USA	60 (Prenatal *n*=15 *vs.* Postnatal *n*=45)	Critical left heart obstruction	Norwood procedure	Hospital stay after operation	Operative mortality	No	All the included cases are from the same research center, with good homogeneity	Reported the gestation age, weight, gender, administration, surgical procedure and subtypes characteristics, etc.	None
Copel[†]	1997	USA	99 (Prenatal *n*=45 *vs.* Postnatal *n*=54)	Mixed types without differences between groups	Univentricular management+ biventricular repair	Hospital stay after operation	Operative mortality	No	All the included cases are from the same research center, with good homogeneity	Reported the gestation age, weight, gender, administration, surgical procedure and subtypes characteristics, etc.	None

*: Contained two studies evaluating the differences between prenatal and postnatal diagnosis for major CHD; †: The types of major CHD were mixed, but there were no significant difference in formation between the two groups; ‡: In short term follow-up, its mortality was treated as operative mortality; §: Some of prenatal diagnosed patients received fetal intervention. All the included studies were retrospectively designed. The qualities of the articles were acceptable. CHD: congenital heart disease; HLHS: hypoplastic left heart syndrome; D-TGA: D-transposition of the great arteries.

model (Fig. 3).

Birth weight

A total of 767 patients from the 7 studies were analyzed.[10,12-15,19] There were no significant differences in birth weight between the two groups (SMD=-0.12, 95%CI, -0.27, 0.04, P=0.14). There was no heterogeneity across the studies (I^2=8%), and the results were analyzed according to the fixed effect model (Table 2).

Apgar score at 1 minute

For the Apgar score at 1 minute evaluation, 375 patients from 4 studies were analyzed.[14,17,19] There were no significant differences in Apgar scores between the two groups (SMD=-0.13, 95%CI, -0.35, 0.08, P=0.22). There was no heterogeneity across the studies (I^2=5%), and the results were analyzed according to the fixed effect model (Table 2).

Apgar score at 5 minutes

For the Apgar score at 5-minute comparison, 474 patients from 5 studies were analyzed.[12,14,17,19] There were no significant differences in Apgar scores between the two groups (SMD=-0.33, 95%CI, -0.67, 0.00, P=0.05). There was heterogeneity across the studies (I^2=66%), and the results were analyzed according to the random effect model (Table 2).

Intubation at birth

For intubation at birth comparison, 198 patients from 3 studies were analyzed.[10,13,19] There were no significant differences in intubation at birth between the two groups (odds ratio=1.75, 95%CI, 0.56, 5.47, P=0.33). There was heterogeneity across the studies (I^2=61%), and the results were analyzed according to the random effect model (Table 2).

Prostaglandin administration

Altogether 907 patients from 5 studies[10,13,14,17,20] were enrolled. There were no significant differences in prostaglandin administration between the two groups (odds ratio=1.31, 95%CI, 0.73, 2.35, P=0.36). There was heterogeneity across the studies (I^2=60%), and the results were analyzed according to the random effect model (Table 2).

Age at operation

For the age at operation evaluation, 610 patients from 6 studies were analyzed:[14,18-21] 175 patients in the prenatal diagnosis group and 435 patients in the postnatal diagnosis group. The mean age at operation for the prenatal and postnatal diagnosis groups ranged from 0.8

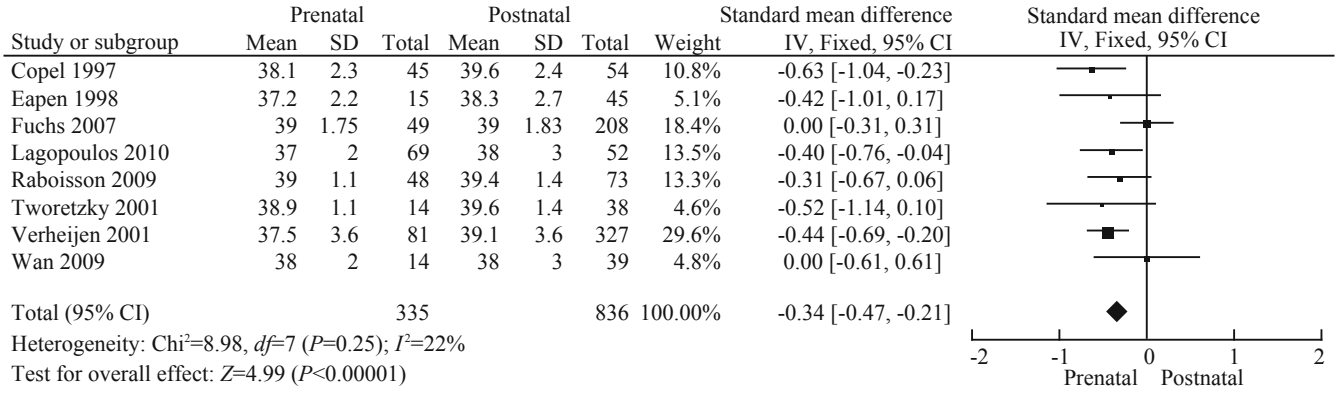

Fig. 3. Forest plot for the comparison of gestation age between the prenatal and postnatal diagnosis groups. Significant difference in operation age was found between the prenatal and postnatal diagnosis groups with a standard mean difference of -0.34 (95% CI, -0.47, -0.21, P<0.00001). CI: confidence interval; *df*: degree of freedom.

Table 2. The meta-analysis results of delivery variables and preoperative management

Variables	Summarized Std. mean difference/odds ratio	Test for overall effect		Test for heterogeneity		
		Z	P	X^2	P	I^2 (%)
Birth weight	-0.12 [-0.27, 0.04]	1.46	0.14	6.51	0.37	8
Apgar score at 1 min	-0.13 [-0.35, 0.08]	1.23	0.22	3.17	0.37	5
Apgar score at 5 min	-0.33 [-0.67, 0.00]	1.95	0.05	11.70	0.02*	66
Intubated preoperational	1.75 [0.56, 5.47]	0.97	0.33	5.13	0.08*	61
Prostaglandins infusion preoperational	1.31 [0.73, 2.35]	0.91	0.36	12.56	0.03*	60

*: Suggested significant heterogeneity among the enrolled studies and random effect model for meta-analysis. Std: standard.

to 7.0 days and from 3.5 to 19.0 days, respectively, and there were significant differences in age at operation between the two groups (SMD=-0.58, 95%CI, -0.76, -0.40, P<0.00001). There was heterogeneity across the studies (I^2=55%), and the results were analyzed according to the random effect model (Fig. 4).

Preoperative mortality

The preoperative mortality was calculated within the period between birth and the first surgical procedure, excluding fetuses terminated and still births. Preoperative mortality comparison revealed that preoperative deaths occurred in 40 (6.72%) of the 595 patients from the 5 studies:[10,14,16,19-21] 7 in the prenatal diagnosis group (3.51%) and 33 in the postnatal diagnosis group (8.33%). There were significant differences in preoperative mortality between the two groups (odds ratio=0.41, 95%CI, 0.18, 0.94, P=0.04). There was no heterogeneity

Study or subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Standard mean difference IV, Fixed, 95% CI
Bonnet 1999	0.8	0.6	57	3.5	8.9	204	38.1%	-0.34 [-0.64, -0.05]
Eapen 1998	2.8	1.9	15	5.5	6.8	45	9.5%	-0.44 [-1.03, 0.15]
Kumar HLHS 1999	2	3.25	27	5	5.75	47	14.2%	-0.59 [-1.08, -0.11]
Kumar TGA 1999	4	2	14	6.5	7.5	28	7.9%	-0.39 [-1.04, 0.26]
Raboisson 2009	7	4	48	19	13	73	21.6%	-1.14 [-1.54, -0.75]
Tworetzky 2001	5.9	1.4	14	8.2	5.1	38	8.6%	-0.51 [-1.13, 0.11]
Total (95% CI)			175			435	100.00%	-0.58 [-0.76, -0.40]
Heterogeneity: Chi²=11.03, *df*=5 (*P*=0.05); I^2=55%								
Test for overall effect: *Z*=6.22 (*P*<0.00001)								

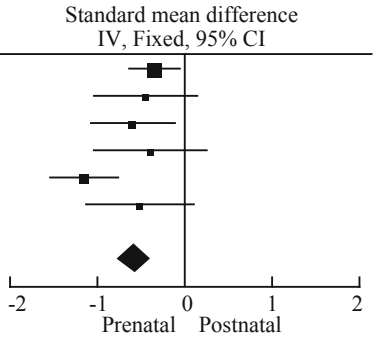

Fig. 4. Forest plot for the comparison of operation age between the prenatal and postnatal diagnosis groups. Significant difference in operation age was found between the prenatal and postnatal diagnosis groups, with a standard mean difference of -0.58 (95% CI, -0.76, -0.40, P<0.00001). Heterogeneity was detected (P=0.05, I^2=55%). HLHS: hypoplastic left heart syndrome; TGA: transposition of great arteries; CI: confidence interval; *df*: degree of freedom.

Study or subgroup	Prenatal Events	Total	Postnatal Events	Total	Weight	Odds ratio M-H, Fixed, 95% CI
TGA						
Bonnet 1999	0	57	15	204	33.8%	0.11 [0.01, 1.80]
Franklin 2002	0	10	10	22	32.3%	0.06 [0.00, 1.09]
Raboisson 2009	1	48	0	73	1.9%	4.64 [0.19, 116.34]
Subtotal (95%CI)		115		299	68.0%	0.21 [0.06, 0.80]
Total events	1		25			
Heterogeneity: Chi²=4.52, *df*=2 (*P*=0.10); I^2=56%						
Test for overall effect: *Z*=2.28 (*P*=0.02)						
LHO						
Eapen 1998	0	15	4	45	11.2%	0.30 [0.02, 5.85]
Subtotal (95% CI)		15		45	11.2%	0.30 [0.02, 5.85]
Total events	0		4			
Heterogeneity: Not applicable						
Test for overall effect: *Z*=0.80 (*P*=0.43)						
DORV						
Lagopoulos 2010	6	69	4	52	20.8%	1.14 [0.31, 4.28]
Subtotal (95% CI)		69		52	20.8%	1.14 [0.31, 4.28]
Total events	6		4			
Heterogeneity: Not applicable						
Test for overall effect: *Z*=0.20 (*P*=0.84)						
Total (95% CI)		199		396	100.0%	0.41 [0.18, 0.94]
Total events	7		33			
Heterogeneity: Chi²=7.11, *df*=4 (*P*=0.13); I^2=44%						
Test for overall effect: *Z*=2.11 (*P*=0.04)						

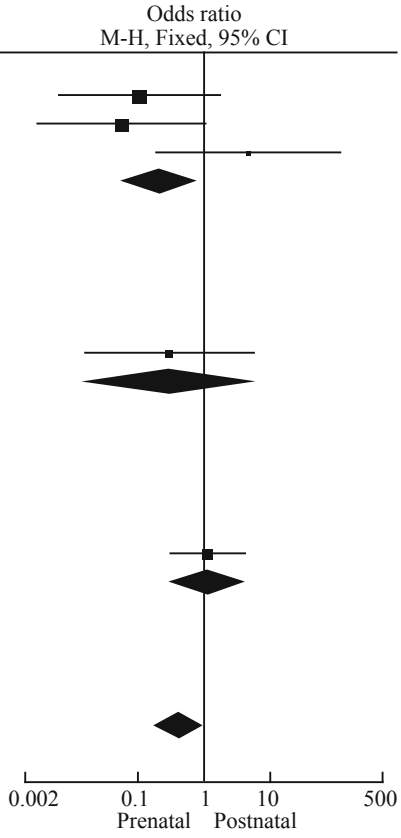

Fig. 5. Forest plot for the comparison of preoperative mortality between the prenatal and postnatal diagnosis groups. Significant difference in preoperative mortality was found between the prenatal and postnatal diagnosis groups, with an odds ratio of 0.41 (95% CI, 0.18, 0.94, P=0.04). No heterogeneity was detected (P=0.13, I^2=44%). TGA: transposition of great arteries; LHO: left heart obstruction; DORV: double outlets right ventricle; CI: confidence interval; *df*: degree of freedom.

across the studies (I^2=44%), and the results were analyzed according to the fixed effect model (Fig. 5). In subgroups analysis, only TGA showed a reduced mortality in the prenatal diagnosis group compared with the postnatal diagnosis group (odds ratio=0.21, 95%CI, 0.06, 0.80, *P*=0.02).

Postoperative mortality

Postoperative mortality was calculated during the hospital stay after the surgical procedure. Postoperative mortality comparison demonstrated that, postoperative deaths occurred in 228 (16.40%) of 1390 patients from 10 studies:[10-12,15,17-21] 55 in the prenatal diagnosis group (14.07%) and 173 in the postnatal diagnosis group (17.32%). There were significant differences in postoperative mortality between the two groups (odds ratio=0.66, 95%CI, 0.46, 0.94, *P*=0.02). There was no heterogeneity across the studies (I^2=30%), and the results were analyzed according to the fixed effect model (Fig. 6). In subgroups analysis, only TGA

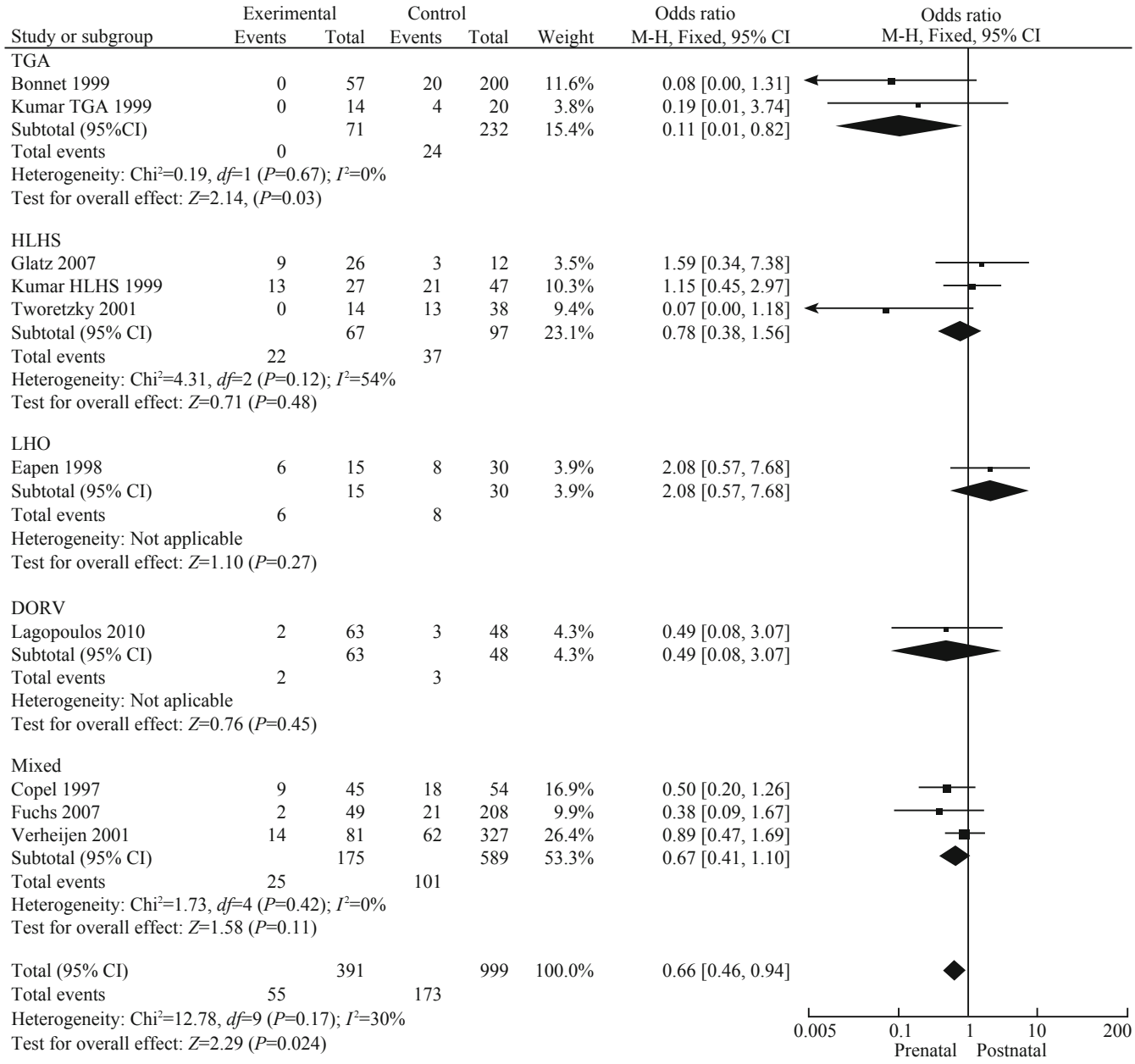

Fig. 6. Forest plot for the comparison of postoperative mortality between the prenatal and postnatal diagnosis groups. Significant difference in postoperative mortality was found between the prenatal and postnatal diagnosis groups, with an odds ratio of 0.66 (95% CI, 0.46, 0.94, *P*=0.02). No heterogeneity was detected (*P*=0.17, I^2=30%). HLHS: hypoplastic left heart syndrome; TGA: transposition of great arteries; LHO: left heart obstruction; DORV: double outlets right ventricle; CI: confidence interval; *df*: degree of freedom.

showed a reduced mortality in the prenatal diagnosis group compared with the postnatal diagnosis group (odds ratio=0.11, 95%CI, 0.01, 0.82, *P*=0.03).

Finally, sensitivity analyses were performed in evaluation of more than 5 studies. The magnitudes and directions of statistical significance of the findings for every analysis were confirmed.

Discussion

Since fetal echocardiography was widely introduced for clinical practice in the 1990s,[22,23] its high accuracy has been confirmed by many studies in collaboration with sectional reviews,[24,25] and the prognostic outcomes from the prenatal diagnosis of CHD have been reported.[26] However, it was reported that an unselected group of prenatal diagnosed cases resulted in a higher mortality,[27] because major CHD could be more easily identified during fetal life.[28,29] Therefore, it was considered unfair to compare major CHD cases with isolated simple ones. To our knowledge, this was the first meta-analysis conducted on the prenatal diagnosis of major CHD by evaluating perinatal management and perioperative mortality. Therefore, this evaluation of prenatal diagnosis provided a better evidence in this field, even in the absence of randomized controlled trials and prospective studies.

Evaluation demonstrated that once the fetuses with major CHD were identified prenatally and complete information about the disease, its therapy and prognosis was obtained, parents could make a choice to terminate or continue the pregnancy. Thus it was impossible to conduct a randomized controlled trial. As randomized control trials could not be conducted, cohort study was an acceptable study design for evaluation. However, prenatal diagnosis would lead to a higher rate of termination of pregnancy;[30] only one study reported the proportion of abortion among the included studies.[18] Although it was not essential to calculate the proportion of cases with termination of pregnancy in retrospective studies, it was still important to provide such data if available. The termination of pregnancy might affect the mortality and morbidity because of the occurrence of terminated cases around the perinatal period with a possibility that the fetuses in more severe conditions would be terminated. Hence, prospective studies were necessary to evaluate the effect of terminated pregnancy especially the formation of CHD types before and after the termination. Another meta-analysis[5] showed that isolated septal defect could be missed prenatally, but could be identified postnatally. However, the spectrum of CHD detected prenatally compared with that detected postnatally seemed to have no significant difference in the included studies with mixed CHD types.[12,15,17]

Effect on perinatal management

Appropriate treatment of newborns with major CHD would improve their prognosis.[31-33] Deliveries with a prenatal diagnosis at a tertiary care institution with expertise in the management of newborns with heart defects allowed for optimal, specific treatment.[13] It was not clear whether this early intervention resulted in a reduced mortality[16] or only simply providing better care and treatment for infants. In our analysis, a fetus with major CHD confirmed by prenatal echocardiography correlated with fewer gestation weeks with a higher proportion of cesarean sections. Should the fetus suffer from severe intrauterine growth restrictions or harmful hemodynamics, which could lead to an abortion,[34,35] the mother could undergo an emergency cesarean section to prevent a worsening outcome. Moreover, most of gestations were higher than or equal to 37 weeks at term by definition. We considered prenatal diagnosis is advantageous in providing an appropriate treatment at an earlier age and avoiding worsening conditions without putting the fetuses facing to a premature delivery at a higher risk. These fetuses would receive a detailed follow-up or examination during their fetal life. The above facts indicated that a slightly shorter gestation for a fetus with major CHD did not place the neonate at extreme risk as no significant premature delivery was identified.

More than 20% of major CHD cases would be sent back home without detection.[19] Intubation in critical CHD was usually performed in cases of apnea secondary to prostaglandin initiation, respiratory distress caused by acidosis/shock and significant pulmonary over-circulation. Given that some lesions included in this study were ductus-dependent, prostaglandin would be helpful. In our analysis, comparison was made to evaluate the proportion of infants receiving intubation and prostaglandin infusion between the two groups and found that there was no significant difference between them. All the cases enrolled for prostaglandin evaluation were duct dependent including those in four studies focused on TGA and one study on DORV. Subgroups analysis showed that there was no significant difference in prostaglandin administration for TGA and DORV, respectively. So it was considered that no radical approach of perinatal intervention and support was given to prenatally diagnosed cases. Upon being arrival or born at the hospital, the treatment of infants with major CHD should be given routinely. The advantage of prenatal diagnosis was to substantially shift intervention to an earlier period of time.

Efficacy on perioperative mortality

Meta-analysis revealed that in most studies surgical

procedures were shifted almost 3 days earlier in prenatally diagnosed cases compared with postnatally diagnosed ones, indicating that the infants might face more challenges when they undergo a procedure earlier. In the prenatal group, however, adequate information could be accumulated for clinical decision-making before birth, and the infants could obtain better perioperative care under better conditions. Early intervention was indicated for the improvement of the conditions or the prevention of further heart or neurological injuries due to hypoxia and harmful hemodynamics.[8] Prenatal diagnosis was valuable in thorough treatment at an early stage, resulting in a better perioperative outcome. However, how to balance the risk of an earlier procedure against the benefit from reversing a continuous hypoxic state remained debated. Moreover, cases of major CHD who were sent back home without detection mostly would return to the hospital under poor conditions (hemodynamic instability). Thus, it was impossible to perform the procedure as early as possible for prenatally diagnosed cases. The pooled results of preoperative mortality confirmed the advantages of prenatal diagnosis in perinatal management. And the postoperative mortality rate during the hospital stay was also significantly lower in the prenatally diagnosed group. Subgroups analysis, however, revealed that only TGA cases had a reduced mortality. Thus TGA cases would benefit from prenatal diagnosis, life-long follow-up should be considered to assess the value of prenatal diagnosis and the quality of life of the surviving cases. Besides, another important point was that some studies demonstrated that the percentage of prenatal diagnosed cases who survived with re-surgery and catheter-free is significant higher than that of postnatal diagnosed ones, and the former had a better preparation or a detailed surgical plan.[15] For other types of major CHD, few studies could be pooled in this meta-analysis and it could not conclude that there was no advantage at all. Because of many factors influencing the long-term prognosis, the benefit and risk of prenatal diagnosis should be evaluated through studies of larger sample size and long-term follow-up. Forbess et al[36] noted that the influence of factors, such as operative techniques and anatomic subtypes, on perioperative mortality might outweigh the less benefits resulted from improved preoperative conditions. However, the results of this meta-analysis revealed that the advantages from prenatal diagnosis especially of TGA cases were identified in the perioperative period. Many studies found the association between CHD and chromosomal abnormalities as well as genetic syndromes. Once children presented with specific syndromes, they might suffer from extra-cardiac malformations and other abnormalities.[37-39] Thus perioperative death would occur as compared with isolated major CHD cases and the results of prenatal diagnosis should be re-evaluated in such cases.[40] However, only three articles[16,20,21] provided such results and different morbidities which could not be pooled. Bonnet et al[20] reported different morbidities and no difference was observed between prenatally and postnatally diagnosed cases. Eapen et al[21] showed a significant reduction of neurological morbidities in prenatal diagnosed cases and Franklin et al[16] reported that prenatal diagnosis could reduce the morbidity of organs except the heart. All of these morbidities were related to the hemodynamics from major CHD. Hence, the early stabilizing hemodynamics, the less morbidity would take place, which indicates the superiority of prenatal diagnosis in reducing morbidities of the disease.

Limitations

There were some limitations in this meta-analysis. The results were pooled from all types of CHD, but similar analysis was also adopted in previous meta-analyses.[8,41] Although meta-regression had been done to evaluate the bias from different types of major CHD in this analysis and proved that lumping different types of CHD made no contribution to heterogeneity, the prognosis of each kind of CHD diverted from each other. Hence, pooling these types of major CHD was to prove the superiority of prenatal diagnosis. This meta-analysis only included limited types of major CHD, and cases of TOF, SV, etc were only presented in the mixed population. Thus the proportion of abnormalities might have some limited bias, and called for further studies on such types of major CHD. Only one study provided the proportion of termination of pregnancy, and the effects of termination need further investigation.

Conclusions

Prenatal diagnosis could reduce perioperative mortality, especially in TGA cases, benefiting from earlier intervention and support for maintaining oxygen saturation, reducing acidosis and allowing earlier resuscitation. Prenatal diagnosis of major CHD is helpful, especially for TGA. Fetal echocardiography should be performed for gravidas with definitive high-risk including maternal diabetes, toxicants exposure during gestation and pregnancy over 40 years of age, etc. More studies are needed to evaluate other types of major CHD and long-term outcomes.

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