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SYSTEMATIC REVIEW AND META-ANALYSIS

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Diagnostic Value of Fetal Echocardiography for Congenital Heart Disease

A Systematic Review and Meta-Analysis

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Abstract: Prenatal diagnosis of fetal congenital heart disease (CHD) has been shown to have a significant effect on prenatal and postnatal management and outcomes. However, the factors influencing its diagnostic accuracy and which section is most adaptive for fetal remain uncertain despite extensive research. The aim of the present study was to evaluate the accuracy of echocardiography for detecting CHD and potential influence factors.

We searched Chinese Biomedical Database (CBM), Medline, ISI Web of Knowledge, the Cochrane Library, and China National Knowledge Infrastructure (CNKI) to identify relevant studies from January 1, 1990 to August 13, 2015.

Overall, the pooled sensitivity, specificity, diagnostic odds ratio, positive likelihood ratio, and negative likelihood ratio were 68.5% (95% confidence interval [CI], 66.8%–70.2%), 99.8% (95% CI, 99.7%–99.8%), 3026.9 (95% CI, 1417.9–6461.8), 659.41 (95% CI, 346.38–1255.3), and 0.246 (95% CI, 0.187–0.324) respectively (AUC = 0.9924). The pooled sensitivity of basic cardiac echocardiographic examination (BCEE), extended cardiac echocardiographic examination (ECEE), BCEE plus outflow tract view (BCEE + OTV), BCEE + OTV + 3VTV (BCEE plus outflow tract view plus three vessel and trachea view) for the prenatal diagnosis of CHD were 49.0%, 75.5%, 66.1%, and 83.7% respectively. The pooled sensitivity of the prenatal echocardiographic diagnosis of CHD during the first trimester, second trimester, the second to third trimester were 60.3%, 60.9%, and 77.4%, respectively. The pooled sensitivity of BCEE and ECEE for the prenatal diagnosis of CHD during the second to third trimester was significantly higher than that during the second trimester. The pooled sensitivity of the prenatal echocardiographic diagnosis of CHD for pregnancies with low risk, high risk, low and high risk, and unselected risk were 45.4%, 85.1%, 89.1%, and 66.2%, respectively. The sensitivity analysis was robust and risk level was significant source of heterogeneity. Deek test indicated no potential significant publication bias.

Prenatal ultrasound is a powerful tool for the diagnosis of CHD; however, echocardiography has individual sensitivity for different gestation period, different levels of risk, and different echo-views.

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Abbreviations: 3VTV = three vessel and trachea view, BCEE = basic cardiac echocardiographic examination, CBM = Chinese Biomedical Database, CHD = congenital heart disease, CNKI = China National Knowledge Infrastructure, ECEE = extended cardiac echocardiographic examination, OTV = outflow tract view.

INTRODUCTION

The incidence of congenital heart disease (CHD) has been estimated at 6 to 12 per 1000 live births.[1] According to the WHO, cardiac defects account for 42% of infant deaths and have become the leading cause of infant mortality.[2] The fetal echocardiogram marks the primary tool for the evaluation and detailed diagnosis of fetal cardiovascular pathology from the late first trimester to term. Prenatal detection of CHD may improve the pregnancy outcome of fetuses with specific types of cardiac lesions.[3] Accurate prenatal diagnosis offers potential clinical benefit with regard to infant outcome.[4] Prenatal detection accuracy have varied widely for CHD.

Some of this variation can be attributed to examiner experience, maternal obesity, transducer frequency, abdominal scars, gestational age, amniotic fluid volume, and fetal position.[5,6] Initially, fetal echocardiography included only a 4-chamber view (basic cardiac echocardiographic examination [BCEE]) of the heart, then outflow tract view (OTV) and 3-vessels trachea view (3VTV) were added to increase accuracy of fetal echocardiography. More recently, ECEE, which included the 4-chamber view, the right ventricular outflow tract, the left ventricular outflow tract, and the main pulmonary artery and its branches,[7] was used as a specific protocol to identify some minimal defects in utero and provide more detail information on suspicious fetal heart. Several subspecialty organizations have published formal practice guidelines.[8–11]

However, there was no consensus as how to choose from the 4 protocols for fetal CHD diagnosis according to different gestation period, different levels of risk, even though some comparison studies[12–17] have been done on the accuracy among different scan protocols. Buskens et al[13] concluded a sensitivity of 4.5% with BCEE in a low-risk populations, whereas Oggè et al[15] concluded a sensitivity of 60.3% with BCEE in a low-risk populations. Ott[12] concluded a sensitivity of 14.3% with ECEE in a low-risk populations, whereas Abdul-Haium et al[17] yielded a sensitivity of 65.8% with ECEE in a low risk. Tegnander et al[16] yielded a sensitivity of 56.7% with BCEE + OTV in an

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unselected populations during the second trimester, where as Zosmer et al[14] yielded a sensitivity of 88.9% with BCEE + OTV in a high-risk population during the second trimester. Previous study[18] had drawn a systematic review using 5 protocols detection of fetal CHD among unselected, low-, and high-risk populations, and they concluded that the pooled sensitivity of BCEE, BCEE + OTV/3VTV, ECEE, and BCEE + OTV + 3VTV were 52%, 65%, 89%, and 90%, respectively; however, they did not evaluate the sensitivity between prospective studies and retrospective studies, and only English articles were included in the study. Besides, they failed to make comparisons among different stages of pregnancy. Therefore, we decided to carry out a meta-analysis of prospective studies to make a more precise estimation. In the meta-analysis, we evaluated the accuracy of fetal diagnosis and compared sensitivities among different diagnostic protocols, different risk factors, and different stages of pregnancy.

MATERIALS AND METHODS

Literature Search

Searches for all relevant published articles were performed in Chinese Biomedical Database (CBM), Medline, ISI Web of Knowledge, the Cochrane Library, and China National Knowledge Infrastructure (CNKI) from January 1, 1990 to August 13, 2015. The language was limited to English or Chinese. The eligibility of every study having >1 author during the search was assessed. We used the following keywords to collect relevant citations: (fetus OR fetal) AND (echocardiography OR echocardiogram OR ultrasonography) AND (congenital heart defect OR congenital heart defects OR congenital heart malformation OR congenital heart abnormality OR congenital heart abnormalities OR CHD) AND (prenatal diagnosis OR prenatal diagnoses OR prenatal screening). We further retrieved reference lists from included articles to avoid missing any relevant studies.

Inclusionand Exclusion Criteria

Two authors independently extracted the following information from included publications: the first author's name, publication year, country, maternal age, risk factors, gestational age, echo-views, number of fetus, and transducer frequency. If there were any disagreements, a consensus was agreed by discussion. Each study was screened for following inclusion and exclusion criteria: prospective studies were included; studies were selected for the review if they included at least 200 pregnant women; All neonates were postnatal examined or autopsy in cases of termination of pregnancy or perinatal death; provided the true positive (TP), true negative (TN), false positive (FP), and false negative (FN) results directly or indirectly, thus allowing the calculation of sensitivity and specificity. Additional data were requested from the original study investigators if necessary, such as positive likelihood ratios and negative likelihood ratios.

Statistical Analysis

We performed meta-analysis in a random-effect/fixed-effect model using Meta-disc software (Version 1.4) and Stata 11.0 software (Stata, College Station, TX). We used symmetric summary receiver-operating curve (SROC) to pool the result of diagnostic tests. Subgroup analysis was further conducted according to different sections, different gestations, and different risk factors. We conducted the heterogeneity test using χ^2-based Q test and I^2 test. The pooled sensitivity and 95% condence interval (CI) were calculated if there was no significant heterogeneity ($P > 0.05$ and $I^2 < 50\%$) existed. If not, a random-effect model was used. In our study, the I^2 value ($0 \sim 100\%$) over 50% indicated significant heterogeneity. The SROCs would show a curvilinear shape existed if a threshold effect appeared. We used funnel plots and the Deek test by Stata 11.0 software to evaluate the publication; a P value >0.05 was considered as no obvious potential publication bias.

RESULTS

Characteristics of the Included Studies

Initial searches identified 2456 English articles and 1456 Chinese articles. According to the inclusion and exclusion criteria mentioned above, 43 articles (18 Chinese article and 25 English articles) including 50 studies were eligible, with a total of 308,029 fetuses (Fig. 1). A summary of included 50 studies is presented in Table 1,[7,12–17,19–54] and the diagnostic test parameter of fetal echocardiography for the prenatal diagnosis of CHD is presented in Table 2.[7,12–14,19–54]

Meta-Analysis

To explore whether any threshold effects existed in our study, we performed a spearman rank correlations of sensitivity against (1-specificity) to detect it. No obvious threshold effects exist in the meta-analysis according to the overall result (Spearman correlation coefficient: 0.041, $P = 0.777$). In general, the overall sensitivity and specificity of fetal echocardiography for the prenatal diagnosis of CHD had a moderate sensitivity of 68.5% (95% CI, 66.8%–70.2%) and the high specificity of 99.8% (95% CI, 99.7%–99.8%) (AUC = 0.9924). The SROC curve is shown in Figure 2 with almost the same specificities of nearly 100%. We divided the included studies into 4 sections according to different echo-views: BCEE, ECEE,

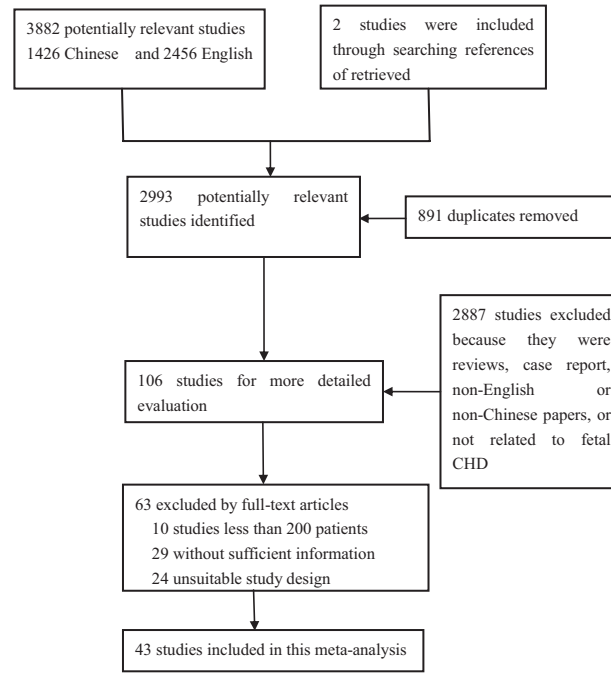

FIGURE 1. Flow diagram of study selection process.

TABLE 1. Characteristics of the 50 Studies Identified

Study/Year	Country	Maternal Age y	Risk Factors	Gestational Ages	Echo-Views	Fetus, n
Levi et al, 1991[19]	Belgium	NP	Low-risk	16–20	ECEE	16,361
Luck, 1992[20]	UK	NP	Unselected	19	BCEE	8523
Vergani et al, 1992[21]	Italy	NP	Unselected	18–20	BCEE	9016
Achiron et al, 1992/a[7]	Israel	25 (18–45)	Low-risk	21 (18–24)	BCEE	5347
Achiron et al, 1992/b[7]	Israel	25 (18–45)	Low-risk	21 (18–24)	ECEE	5347
Achiron et al, 1994[22]	Israel	NP	Low-risk	13-15	ECEE	660
Kirk et al, 1994[23]	USA	NP	Low-risk	23 (14–42)	BCEE	5967
Ott, 1995/a[12]	USA	NP	High-risk	15–40	BCEE + OTV	886
Ott, 1995/b[12]	USA	NP	Low-risk	15–40	BCEE + OTV	1136
Hsieh et al, 1996[24]	Chinese Taipei	NP	Low- and high-risk	16–36	ECEE	2485
Buskens et al, 1996[13]	Netherlands	29 (14–47)	Low-risk	19 (16–24)	BCEE	5319
Zhou et al, 1996[25]	PR China	28 (24–37)	High-risk	20–40	ECEE	368
Kirk et al, 1997[26]	USA	NP	Unselected	18 (14–42)	BCEE + OTV	16,121
Todros et al, 1997[27]	Italy	NP	Low-risk	19–22	BCEE	8299
Stefos et al, 1999[28]	Greece	NP	Unselected	18–22	BCEE	7236
Zosmer et al, 1999[14]	UK	NP	High-risk	17–22	BCEE + OTV	323
Pan et al, 2001[29]	PR China	22–39	High-risk	20–42	ECEE	900
Comas Gabriel wt al, 2002[30]	Spain	17–46	High-risk	14.2 (12–17)	ECEE	334
Ozkutlu et al, 2005[31]	Turkey	28 (18–42)	High-risk	18–39	ECEE	642
Zhou et al, 2005/a[32]	PR China	NP	High-risk	12–17	BCEE	383
Zhou et al, 2005/b[32]	PR China	NP	High-risk	12–17	BCEE + DV	383
Liu et al, 2005/a[33]	PR China	26–36	NP	16–40	ECEE	4300
Liu et al, 2005/b[33]	PR China	26–36	NP	16–40	BCEE	4300
Becker et al, 2006[34]	Germany	35 (15–46)	Low- and high-risk	11–13	ECEE	3094
Oggè et al, 2006/a[15]	Italy	NP	Low-risk	18–24	BCEE	6368
Oggè et al, 2006/b[15]	Italy	NP	Low-risk	18–24	BCEE + OTV	6368
Tegnander et al, 2006[16]	Norway	29 (15–53)	Unselected	18 (16–22)	BCEE + OTV	29,460
Zhu et al, 2006[35]	PR China	30 (20–48)	High-risk	26.5 (16–42)	ECEE	1788
Plesinac et al, 2007[36]	Serbia	19–48	High-risk	NP	ECEE	517
Chang et al, 2008[37]	PR China	29 (21–37)	Unselected	20–26	ECEE	1200
Chen et al, 2008 [38]	PR China	16–45	Low- and high-risk	16–42	ECEE	17651
Ren et al, 2008/a[39]	PR China	29 ± 6	Unselected	20–24	BCEE	11544
Ren et al, 2008/b[39]	PR China	29 ± 6	Unselected	20–24	BCEE + OTV	11544
Thangaroopan et al, 2008[40]	Canada	28	High risk	21 (16–37)	ECEE	276
Wu et al, 2009/a[41]	PR China	30 (20–40)	Unselected	20–24	BCEE	8025
Wu et al, 2009/b[41]	PR China	30 (20–40)	Unselected	20–24	BCEE + OTV + 3VTV	8025
Xu et al, 2009[42]	PR China	28 (18–48)	Unselected	18–40	BCEE + OTV + 3VTV	4882
Bennasar et al, 2010[43]	Spain	32 (16–43)	High-risk	24 (11–41)	ECEE	342
Huang et al, 2010[44]	PR China	22–40	Low- and high-risk	21–40	ECEE	6500
Yan et al, 2010[45]	PR China	18–43	Low- and high-risk	20–41	BCEE + OTV + 3VTV	4200
Zhao et al, 2010[46]	PR China	NP	Unselected	20–40	ECEE	6621
Yagel et al, 2011[47]	Israel	NP	Low- and high-risk	14–24	ECEE	13,101
Abdul Haium et al, 2011[17]	UK	NP	Low-risk	19–22	BCEE + OTV	64,681
Zeng et al, 2011[48]	PR China	19–41	Low- and high-risk	16–36	BCEE	293
Prats et al, 2012[49]	Spain	33 (17–55)	Low-risk	11–13	BCEE + DV	9483
Luan et al, 2012[50]	PR China	20–37	Unselected	16–41	BCEE + OTV + 3VTV	9237
Wang et al, 2012[51]	PR China	20–40	Low- and high-risk	20–24	BCEE + OTV + 3VTV	8481
Wang et al, 2012[52]	PR China	17–46	Unselected	15–40	BCEE + OTV + 3VTV	3095
Wang et al, 2014[53]	PR China	20–35	Unselected	18–28	ECEE	1500
Wiechec et al, 2015[54]	Poland	32.3 (27–40)	Unselected	11–13	BCEE	1084

3VTV = 3-vessel and trachea view, BCEE = basic cardiac echocardiographic examination, DV = venous duct, ECEE = extended cardiac echocardiographic examination, NP = not provided, OTV = outflow tract view.

TABLE 2. The Diagnostic Test Parameter of Fetal Echocardiography for the Prenatal Diagnosis of CHD

Study/Year	TP/n	FP/n	FN/n	TN/n	SEN/%	SPE/%	Transducer Frequency
Levi et al, 1991[19]	154	8	227	15,972	40.4	99.9	NP
Luck, 1992[20]	9	2	16	8498	36	100	3.5, 5.0 MHz
Vergani et al, 1992[21]	33	2	14	8967	70.2	100	3.5, 5.0 MHz
Achiron et al, 1992/a[7]	11	1	12	5323	47.8	100	3.5, 5.0 MHz
Achiron et al, 1992/b[7]	18	1	5	5323	78.3	100	3.5, 5.0 MHz
Achiron et al, 1994[22]	3	0	6	651	33.3	100	6.5, 7.5 MHz
Kirk et al, 1994[23]	24	1	27	5915	47.1	100	NP
Ott, 1995/a[12]	10	2	6	868	62.5	99.8	NP
Ott, 1995/b[12]	2	12	12	1110	14.3	98.9	NP
Hsieh et al, 1996[24]	67	2	3	2413	95.7	99.9	3.5, 5.0 MHz
Buskens et al, 1996[13]	2	5	42	5270	4.5	99.9	3.5, 3.75 MHz
Zhou et al, 1996[25]	10	1	1	356	90.9	99.7	3 MHz
Kirk et al, 1997[26]	73	12	38	15,998	65.8	99.9	NP
Todros et al, 1997[27]	6	6	34	8253	15	99.9	NP
Stefos et al, 1999[28]	14	2	17	7203	45.2	100	3.5, 3.75 MHz
Zosmer et al, 1999[14]	24	0	3	296	88.9	100	NP
Pan et al, 2001[29]	34	43	3	820	92	95	2.5–3.5 MHz
Comas Gabriel et al, 2002[30]	38	0	10	286	79.2	100	NP
Ozkutlu et al, 2005[31]	42	0	3	597	93.3	100	2.5, 5.0 MHz
Zhou et al, 2005/a[32]	18	1	12	352	60	99.7	3.5, 6.9 MHz
Zhou et al, 2005/b[32]	25	1	5	352	83.3	99.7	3.5, 6.9 MHz
Liu et al, 2005/a[33]	46	4	5	4245	90.2	99.9	3.5 MHz
Liu et al, 2005/b[33]	33	4	18	4245	64.7	99.9	3.5 MHz
Becker et al, 2006[34]	32	0	6	3056	84.2	100	8.0, 14.0 MHz
Oggè et al, 2006/a[15]	35	14	23	6296	60.3	99.8	NP
Oggè et al, 2006/b[15]	38	16	20	6294	65.5	99.7	NP
Tegnander et al, 2006[16]	55	1	42	29362	56.7	100	3.5, 5.0 MHz
Zhu et al, 2006[35]	35	1	3	1749	92.1	99.9	3.5, 5.0 MHz
Plesinac et al, 2007[36]	68	1	4	444	94.4	99.8	NP
Chang et al, 2008[37]	9	0	1	1190	90	100	3.5 MHz
Chen et al, 2008[38]	129	5	18	17,499	87.8	100	3.5 MHz
Ren et al, 2008/a[39]	33	2	21	11,488	61.1	99.9	5 MHz
Ren et al, 2008/b[39]	48	2	6	11,488	88.9	99.9	5 MHz
Thangaroopan et al, 2008[40]	4	6	35	231	10.3	97.5	3.5, 7.5vMHz
Wu et al, 2009/a[41]	21	4	11	7989	65.6	99.9	3.5, 5.0 MHz
Wu et al, 2009/b[41]	26	4	6	7989	81.3	99.9	3.5–5 MHz
Xu et al, 2009[42]	50	1	23	4808	68.5	100	3.5, 5 MHz
Bennasar et al, 2010[43]	172	17	3	150	98.3	89.8	4–8 MHz
Huang et al, 2010[44]	61	212	3	6224	95.3	96.7	1–5 MHz, 2–4 MHz
Yan et al, 2010[45]	37	4	6	4153	86.1	99.9	2–6 MHz
Zhao et al, 2010[46]	12	6	1	6602	92.3	99.9	4–6 MHz
Yagel et al, 2011[47]	169	0	24	12,908	87.6	100	5.0–12.0 MHz
Abdul-Haium et al, 2011[17]	131	0	68	64,482	65.8	100	NP
Zeng et al, 2011[48]	9	0	5	279	64.3	100	4–5 MHz
Prats et al, 2012[49]	6	408	42	9027	12.5	95.7	NP
Luan et al, 2012[50]	37	0	4	9196	90.2	100	2–5 MHz, 1–5 MHz, 4–8 MHz
Wang et al, 2012[51]	66	1	5	8409	93	100	NP
Wang et al, 2012[52]	35	1	5	3054	87.5	99.9	2.5–6 MHz
Wang et al, 2014[53]	13	2	2	1483	86.7	99.9	NP
Wiechec et al, 2015[54]	35	0	42	1007	45.7	100	4–8 MHz, 5–9 MHz

CHD = congenital heart disease, FN = false negatives, FP = false positives, NP = not provided, TN = true negatives, TP = true positives.

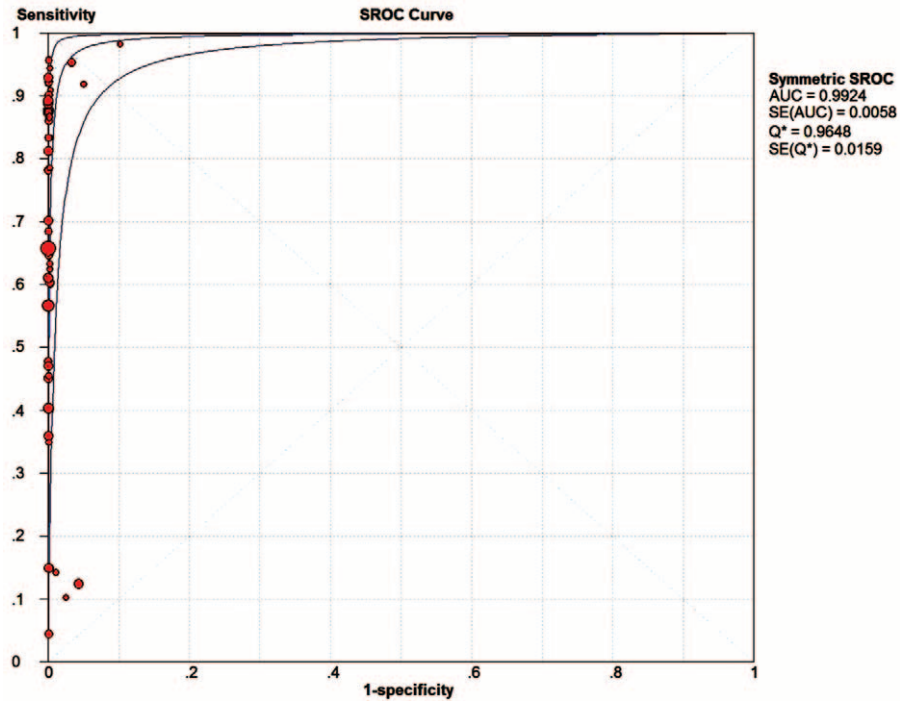

FIGURE 2. The SROC curve of echocardiography for the prenatal diagnosis of CHD. AUC = area under curve, CHD = congenital heart disease, SROC = summary receiver-operating characteristic.

BCEE + OTV, and BCEE + OTV + 3VTV. We divided the eligible studies into 3 sections according to gestation order: the first trimester, the second trimester, the second to third trimester. And we also divided the eligible studies into 4 sections according to different risk factors: low risk, high risk, low and high risk, and unselected risk. The overall sensitivity of BCEE (Fig. 3A), BCEE + OTV (Fig. 3B), ECEE (Fig. 3C), BCEE + OTV + 3VTV (Fig. 3D) were 49.0%, 66.1%, 75.5%, and 83.7%, respectively. The overall sensitivity of ECEE, BCEE + OTV, and BCEE + OTV + 3VTV screening for fetal CHD was obviously higher compared with the echo-views of BCEE ($\chi^2 = 133.14, 34.506, 99.337$, all $P < 0.05$, respectively). When compared with BCEE + OTV, the overall sensitivity of ECEE was also obviously higher ($\chi^2 = 18.168$, $P < 0.05$). And when compared with BCEE + OTV and ECEE, the overall sensitivity of BCEE + OTV + 3VTV was also obviously higher ($\chi^2 = 30.134, 9.447$, $P < 0.05$, $P = 0.002$, respectively).

Twenty-three articles diagnosed fetal CHD during the second trimester, 20 articles diagnosed fetal CHD during the second to third trimester, 2 articles diagnosed fetal CHD during first trimester to second trimester, 3 articles diagnosed fetal CHD during first trimester, only 1 article diagnosed fetal CHD during whole trimester, and 1 article not provided the gestation. According to different gestations, we performed a layering research and sensitivity analysis on the BCEE, ECEE, BCEE + OTV, BCEE + OTV + 3VTV. The overall sensitivity of the 4 protocols during the second trimester to third trimester were 65.6% (95% CI, 57.5%–73.0%), 60.3% (95% CI 51.7%–68.4%), 84.9% (95% CI 81.4%–88.0%), 80.7% (95% CI 74.5%–86.0%), respectively, and during the second trimester, the overall sensitivity of the 4 sections were 47.4% (95% CI 42.3%–52.5%), 68.0% (95% CI 63.4%–72.4%), 58.4% (54.4%–62.3%), 89.3% (81.7%–94.5%), respectively. When compared with the second trimester, the overall sensitivity of BCEE (Fig. 4) and ECEE (Fig. 5) screening for fetal CHD during the second to third trimester was obviously higher ($\chi^2 = 14.585, 90.386$, $P < 0.05$, respectively). However, when compared with the second trimester, the overall sensitivity of BCEE + OTV and BCEE + OTV + 3VTV screening for fetal CHD during the second to third trimester was not statistically significant ($\chi^2 = 2.865, 3.548$, $P = 0.091, 0.06$, respectively).

To explore the sensitivity between the 4 scan protocols and 4 risk factors (low, high, low and high, unselected), we performed a layering research. In general, the overall sensitivity of BCEE, BCEE + OTV, ECEE, and BCEE + OTV + 3VTV for whole pregnancies were 49.0% (95% CI, 44.9%–53.2%), 66.1% (95% CI, 62.1%–70.0), 75.5% (95% CI, 73.2%–77.6%), and 83.7% (95% CI, 790%–87.7%), respectively. For pregnancies with low-risk factors and unselected factors, the overall sensitivity of BCEE (Fig. 6) was 36.1% (95% CI, 29.7%–42.9%) and 55.7% 95% CI, 49.1%–62.2%), respectively. Only one article[32] studied BCEE for pregnancies with high-risk factors, and only 1 article[48] studied BCEE for pregnancies with low and high factors. For pregnancies with low-risk factors, high risk factors (Fig. 7), low- and high-risk factors (Fig. 8), the overall sensitivity of ECEE was 43.1% (95% CI, 38.5%–47.8%), 86.7% (95% CI, 83.2%–89.6%), and 89.5% (95% CI, 86.5%–92.0%), respectively. Only 2 articles[37,46] studied ECEE for pregnancies with unselected factors. For pregnancies with low-risk factors and unselected factors, the overall sensitivity of BCEE + OTV was 63.1% (95% CI, 57.1%–68.9%) and 67.2% (95% CI, 61.1%–72.8%), respectively. Only 1 article[14] studied BCEE + OTV for pregnancies with

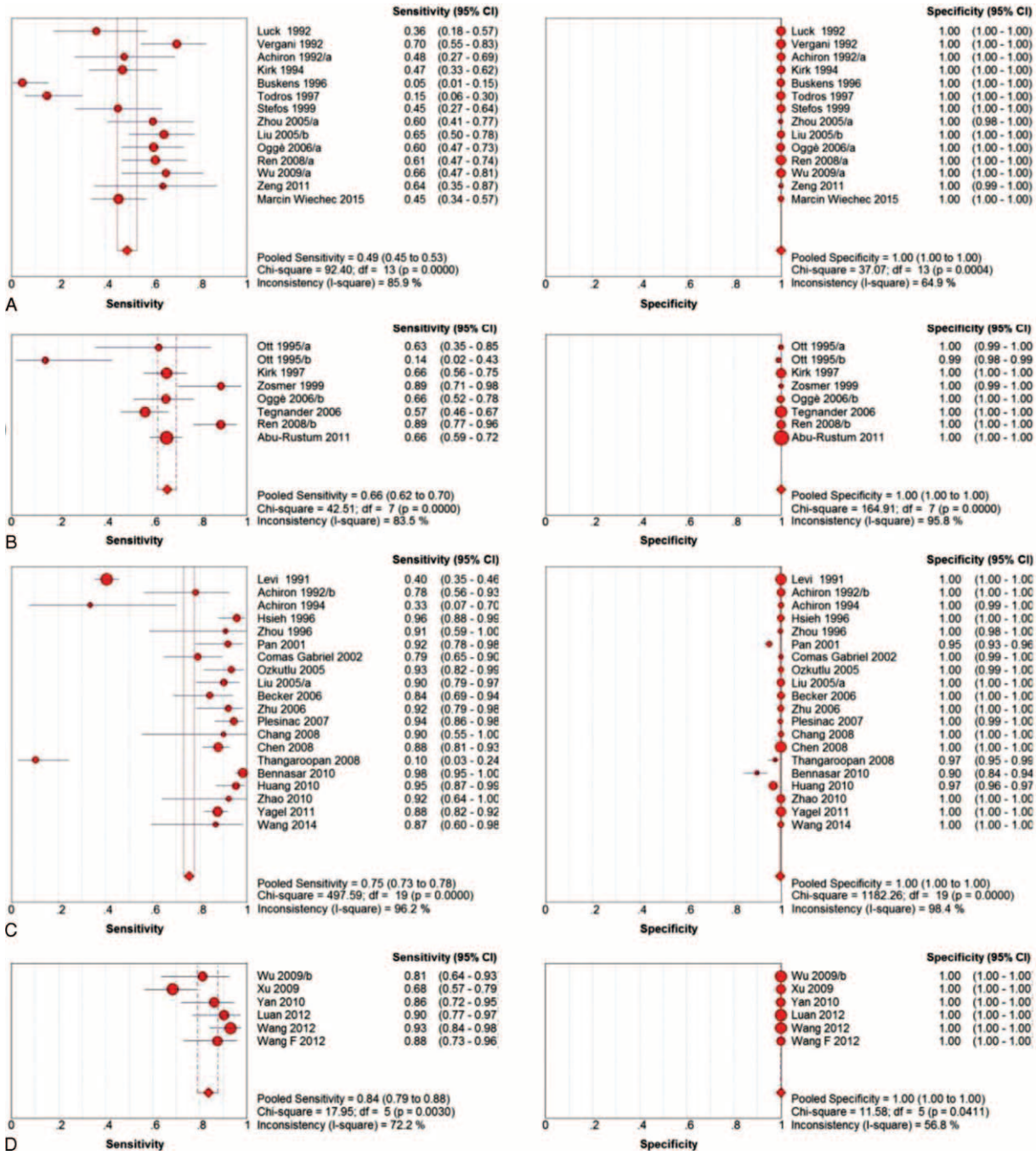

FIGURE 3. The pooled sensitivity and specificity of BCEE (A), BCEE + OTV (B), ECEE (C), BCEE + OTV + 3VTV (D) for the prenatal diagnosis of CHD. 3VTV = three vessel and trachea view, BCEE = basic cardiac echocardiographic examination, CHD = congenital heart disease; CI = confidence interval, ECEE = extended cardiac echocardiographic examination, OTV = outflow tract view.

high risk-factors, but no article for low- and high-risk factors. Three articles discussed BCEE + OTV + 3VTV for pregnant women with unselected risk factors, the overall sensitivity was 77.4% (95% CI, 69.7%–83.9%).

Then a χ^2 test was performed between 4 scan protocols and different risk factors. Compared with pregnancies with low risk factors, the overall sensitivity of BCEE for whole pregnancies was obvious higher ($\chi^2 = 10.605$, $P = 0.001$). Compared with pregnancies with low-risk factors, the overall sensitivity of ECEE for whole pregnancies was also higher ($\chi^2 = 133.827$, $P < 0.05$), and for pregnancies with high-risk factors and low- and high-risk factors, the overall sensitivity of ECEE was obviously higher when compared with whole pregnancies ($\chi^2 = 33.670$, 54.686, $P < 0.05$, respectively).

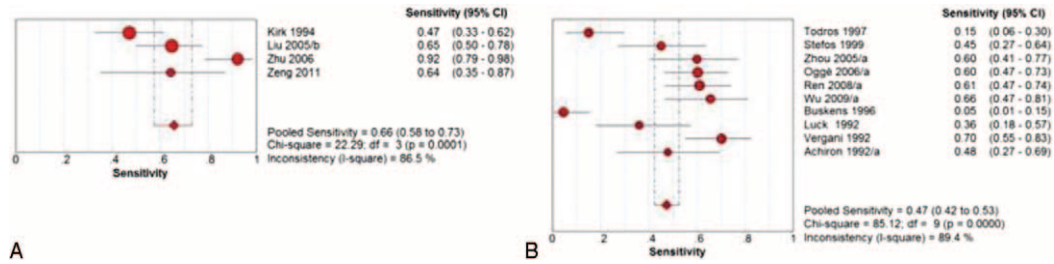

FIGURE 4. The pooled sensitivity of BCEE for the prenatal diagnosis of CHD during the second trimester (A) and the second to third trimester (B). BCEE = basic cardiac echocardiographic examination, CHD = congenital heart disease, CI = confidence interval.

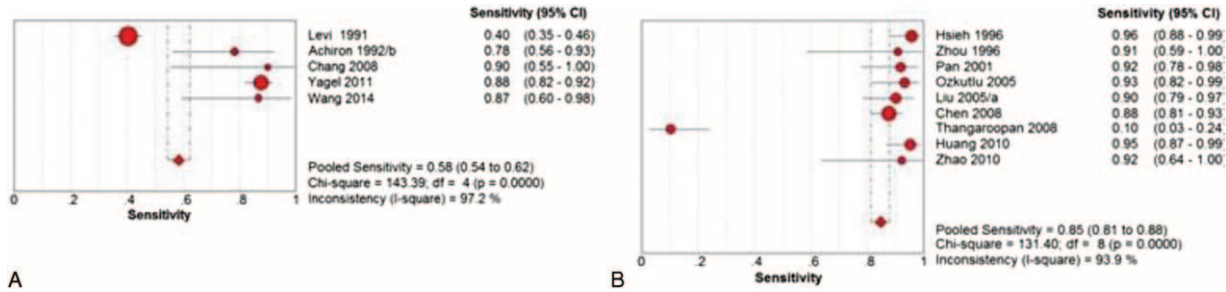

FIGURE 5. The pooled sensitivity of ECEE for the prenatal diagnosis of CHD during the second trimester (A) and the second to third trimester (B). CHD = congenital heart disease, CI = confidence interval, ECEE = extended cardiac echocardiographic examination.

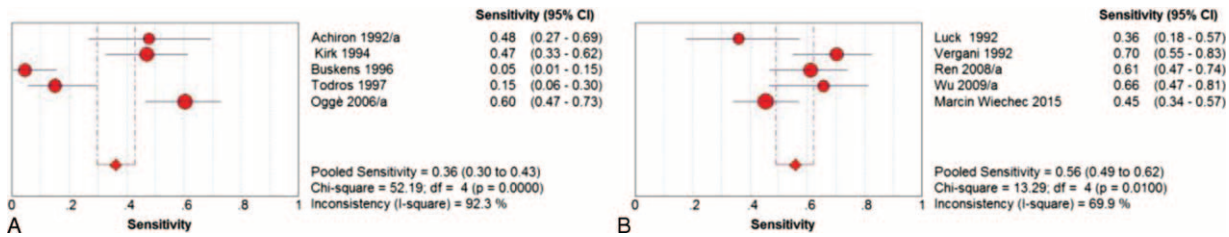

FIGURE 6. The pooled sensitivity of BCEE for pregnant women with low-risk factors (A) and unselected factors (B). BCEE = basic cardiac echocardiographic examination, CI = confidence interval.

However, the overall sensitivity of BCEE + OTV for whole pregnant women was not statistically significant than pregnancies with low-risk factors and unselected risk factors ($\chi^2 = 0.799, 0.069$, $P = 0.371, 0.793$, respectively). Compared with pregnancies with unselected risk factors, the overall sensitivity of BCEE + OTV + 3VTV for whole pregnant women was not statistically significant ($\chi^2 = 1.963$, $P = 0.161$). Likewise, the overall sensitivity of BCEE was not statistically significantly than that of whole pregnancies ($\chi^2 = 2.998$, $P = 0.083$).

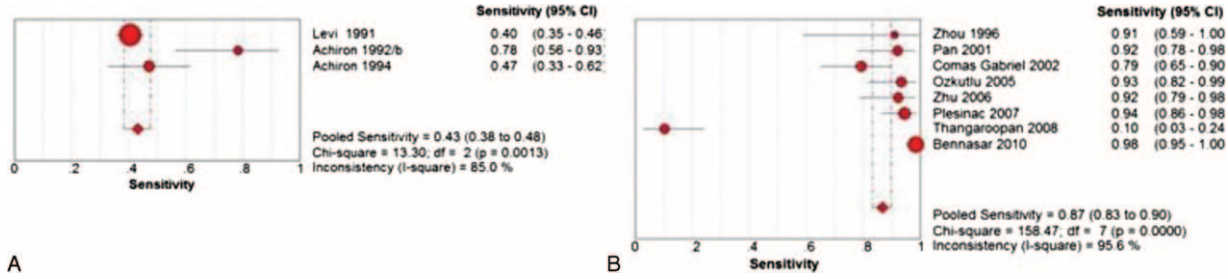

FIGURE 7. The pooled sensitivity of ECEE for pregnant women with low-risk factors (A) and high-risk factors (B). CI = confidence interval, ECEE = extended cardiac echocardiographic examination.

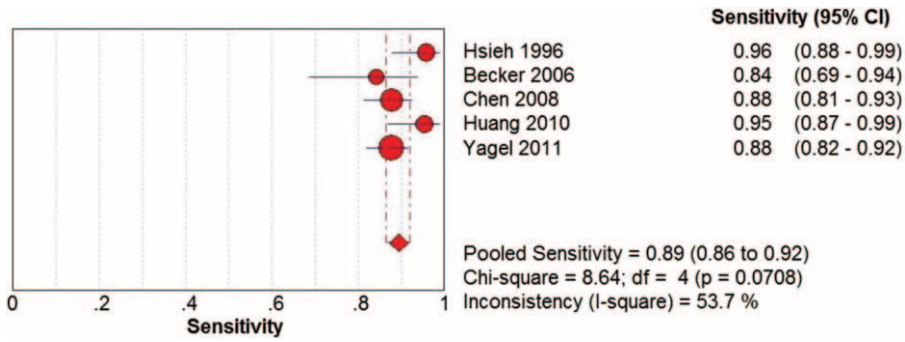

FIGURE 8. The pooled sensitivity of ECEE for pregnant women with low- and high-risk factors. CI = confidence interval, ECEE = extended cardiac echocardiographic examination.

Sensitivity Analysis and Meta-Regression

There was substantial diversity across studies, the inconsistency (I^2) was 94.5%, and sensitivity was 68.5% (95% CI, 66.8%−70.2%). One set of study data[7,12,16,19–20,22–23,32,40,49] were systematically removed, and the pooled results for the remaining studies were rechecked whether the results had a significant change, the inconsistency was still between 94.0% and 94.6%, then we removed them all, the inconsistency was still 85%, which suggested that the sensitivity analysis was robust. Then the sensitivity analysis was conducted for every study. If substantial heterogeneity is found to be present, then reasons for such heterogeneity can be explored by relating study level covariates to an accuracy measure. So a meta-regression was performed, out of all of the parameters, the risk level was significant sources of heterogeneity ($P = 0.012$). However, none of the country, echo-view, transducer frequency, publication year, and gestation were statistically significant sources of heterogeneity ($P > 0.05$). The meta-regression analysis results were shown in Table 3.

Publication Bias

We used funnel plot to detect whether the potential the publication bias of included studies existed in this study. In funnel plots, each dot represents a study included. All dots symmetric distribution on both sides of the line suggested there was no obvious publication bias. If not, which indicated that publication bias was existed. An absence of any asymmetric distribution of data points in the funnel plot and a quantified result of $P = 0.061$ in the Deek test indicated no potential significant publication bias in our meta-analysis (Fig. 9).

TABLE 3. Meta-Regression (Inverse Variance Weights, n = 50)

Var	Coeff.	Std. Err.	*P*	RDOR	95% CI
Cte.	3.933	2.0139	0.0575	—	—
S	−0.275	0.1623	0.0980	—	—
Country	−0.384	0.6173	0.5373	0.68	(0.20, 1.96)
Echo-view	0.026	0.3221	0.9359	1.03	(0.54, 1.97)
Frequency	−0.003	0.0797	0.9715	1.00	(0.85, 1.17)
Year	0.041	0.0612	0.5081	1.04	(0.92, 1.18)
Gestation	0.221	0.3496	0.5313	1.25	(0.62, 2.52)
Risk level	0.728	0.2775	0.0120	2.07	(1.18, 3.63)

CI = confidence interval.

DISCUSSION

The results of this meta-analysis indicate that prenatal echocardiography for CHD diagnosis had a moderate sensitivity and high specificity. The areas under the curve of the SROC curves for all data sets were >0.9924, which demonstrated a quite high diagnostic accuracy, regardless of the methodology variation and sample origin. It is reported that fetal echocardiography using as a clinical technique for the prenatal diagnosis of CHD was appeared in the early 1980s,[27] and from then on numbers of studies aimed at assessing its accuracy for CHD.[7,13,21,23,55] However, their results are inconsistent. Most future parents have great expectations from echocardiography screening for CHD and missed diagnoses often lead to legal action. Therefore, it is important to define the accuracy of echocardiography in pregnancies for CHD. Our study was designed for this purpose.

As the most basic ultrasound method, BCEE plays an important role in screening for fetal malformations. However, our study showed that the overall sensitivity and specificity were 49.0% and 99.9%, respectively. The overall sensitivity was lower compared with ECEE, BCEE + OTV, and BCEE + OTV + 3VTV, which increased chances of missed diagnosis. The reasons perhaps as follows[56]: unclear image caused because of gestational age, limited resolution, transducer frequency, timing of examination, fetal position, and maternal factors; when the discrepancy of 4-chamber size is not obvious, such cardiac abnormalities as aortic coarctation and ventricular dysplasia maybe missed diagnosis; part of the cardiac abnormalities in pregnancy is progressive development, and they cannot be detected readily during the first and second trimester, such as aorta or pulmonary artery stenosis; part of the conotruncal defects manifest as normal 4-chamber size. In addition, we hold that the BCEE does not directly evaluate the great vessels, which is another important factor. We obtained a 66.1% sensitivity by BCEE + OTV, compared with 49.0% sensitivity with BCEE alone. Adding visualization of the ventricular outflow tracts to the assessment of the 4-chamber view has been suggested as likely to increase the sensitivity of ultrasound screening for major CHD.[7,57] However, left and right ventricular outflow tract detection technology is not easy to master and to learn, and it is often time-consuming.[58] To compensate for this weakness of BCEE, we added 3VTV to our routine fatal echocardiography protocol.[59] Studies incorporating the 3VTV into screening obstetric examinations have also increased the detection of CHD.[56] In our study, we obtained a sensitivity of 83.7% by BCEE + OTV + 3VTV. Addition of the outflow tracts and 3 vessels with trachea view can increase sensitivity

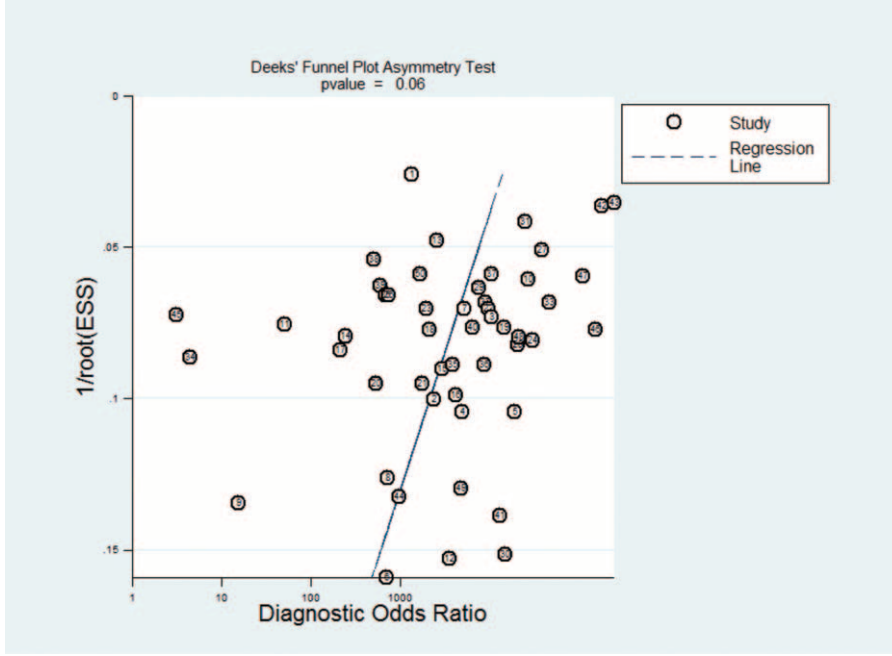

FIGURE 9. Publication bias was tested using funnel plots and the Deek test.

to as high as 90%.[23,60,61] We obtained a 75.5% sensitivity by ECEE and conformed that ECEE had advantages in sensitivity ($\chi^2 = 133.14$, $P < 0.05$) compared with BCEE, so ECEE should be highlighted for fetal echocardiography.

Early screening of fetal CHD is vital for perinatal period health care and improving the prognosis of neonatal; furthermore, it can also promote the rapid development of fetal CHD treatment technology. What is more, earlier screening of fetal CHD can provide parents an opportunity to a safe termination of pregnancy or make a choice to karyotype analysis or genetic counseling. For parents who are at risk for having a CHD child, the finding of normal cardiac anatomy can relieve their anxious during early-stage per pregnancy.[62] Even previous systematic review using 5 protocols detection of fetal CHD among unselected, low, high risk populations; however, they did not evaluate the sensitivity of different stages of pregnancy with different protocols.[18] In our study, only 3 articles[34,49,54] study the fetal CHD during the first trimester, so we could not make a specific comparison among different echocardiography protocols. The pooled sensitivity of the first trimester was 60.3%, compared with 77.4% of the second to third trimester; this is perhaps because of both the distance of the fetus from the maternal abdominal wall and the small size of the heart structures,[63] so early fetal echocardiography should always be followed by echocardiography at second trimester and third trimester.[14,64,65] Our findings suggested that during the second trimester, BCEE and ECEE had a higher sensitivity of 47.4% and 58.4%, respectively. With the advancing of gestational age, the sensitivity of BCEE and ECEE increased to 65.6% and 84.9%, respectively. Although certain types of fetal CHD can be detected after 13 weeks of pregnancy, fetal echocardiography for screening of pregnancies at risk for CHD generally should be performed at 18 to 22 weeks of gestation.[1,66]

Our finding suggested that, compared with the low risk population by BCEE, the unselected risk population received more benefit from screening of fetal CHD. Likewise, the high-risk, low- and high-risk population received more benefit from prenatal fetal CHD screening when compared with unselected populations.[65] However, for BCEE + OTV and BCEE + OTV + 3VTV, they did not receive more benefit from prenatal screening ($P > 0.05$). We also find that, compared with BCEE among the low-risk populations, ECEE yielded a higher sensitivity, similary, when compared with low-risk populations and ECEE for high-risk populations yielded a higher sensitivity, which perhaps because the pregnant women with high-risk factors had a high risk of delivering a fetus with CHD. Thus, ECEE had a higher sensitivity compared with BCEE; this result coincides with the results of previous meta-analysis. However, there were only 23 prospective studies in their meta-analysis, whereas 50 prospective studies were involved in our meta-analysis. According to the regression analysis results, we find that among all related variables, the risk levels were an independent predictor of the sensitivity of a CHD diagnosis. Inevitably, there are also some limitations in this meta-analysis. Our study was based on pooled data; substantial variation will continue to exist, despite any subgroup analysis. Besides, the power to detect differences among subgroups may have been limited by the small number of studies in specific subgroups.

CONCLUSIONS

In conclusion, our study has shown it is highly effective to perform prenatal fetal CHD echocardiography screening for its moderate sensitivity and particularly higher specificity. We also find that with the population risk factor advances, progression in gestational age, extension of the echo-views, combination of echocardiographic approaches, and promotion of the echocardiographic modality, the diagnostic sensitivity of fetal CHD was significantly increased.[67] Furthermore, prenatal fetal CHD echocardiography screening result should not based on any single ultrasonic modality. As a result of the limitation of literature relevant, further large-scale multicenter prospective studies are warranted.

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