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REVIEW ARTICLE

Maternal Reproductive History and the Risk of Congenital Heart Defects in Offspring: A Systematic Review and Meta-analysis

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Abstract Epidemiological studies have reported conflicting results on the association of congenital heart defect (CHD) risk in offspring with a maternal history of prior pregnancies and abortions, but no meta-analysis has been reported. We searched MEDLINE and EMBASE from their inception to April 14, 2014, for relevant studies that assessed the association between maternal reproductive history and CHD risk. Two authors independently assessed eligibility and extracted data. Fixed-effects or random-effects models were used to calculate the pooled odds ratios (ORs). Among 1,599 references, 17 case–control studies and one nested case–control study were included in this meta-analysis. The summary OR for the ever versus nulligravidity was 1.18 (95 % CI 1.03–1.34). A dose–response analysis also indicated a positive effect of maternal gravidity on CHD risk, and the summary OR for each increment in number of pregnancies was 1.13 (95 % CI 1.08–1.18). A history of abortion was associated with a 24 % higher risk of CHD, OR = 1.24 (95 % CI 1.11–1.38). When stratified by abortion category, CHD risk increased by 18 and 58 % with a history of spontaneous abortion and induced abortion, respectively. The summary OR for each increment of one abortion was 1.28 (95 % CI 1.18–1.40). In summary, this study provides evidence that increased maternal gravidity was positively associated with a risk of CHDs in offspring. Meanwhile, our results demonstrate a positive association of any history of abortion with an increased risk of CHDs.

Keywords Congenital heart defects · Maternal reproductive history · Gravidity · Abortion · Dose–response

Yu Feng and Song Wang have contributed equally to this work and should be considered co-first authors.

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Introduction

Congenital heart defects (CHDs) are the most common human birth defects and the leading cause of perinatal mortality, with an incidence of approximately 6–8 per 1,000 live births or even higher [22]. The etiology of CHD is complex and probably involves the interaction of environmental exposures and inherited factors [45]. A multitude of research studies have identified both chromosomal as well as genetic mutations as causative factors for syndromic heart malfunction [32], but the origin of non-syndromic CHD, which accounts for most congenital cardiac abnormalities, is still unknown.

Maternal phenylketonuria, diabetes mellitus, maternal teratogen exposure, and maternal therapeutic drug exposure during pregnancy may increase the risk of congenital malformations in offspring [23]. Apart from these influences, previous studies have indicated that a maternal history of prior pregnancies and abortions may predispose to certain categories of congenital defects. Gravidity is defined as the number of previous pregnancies. With 12–24 % of all clinically recognized pregnancies ending in abortion, abortions are the most common complication

during pregnancy [16, 48]. While the gestational boundary for abortion has no standard definition internationally, most abortions occur within the first 12 weeks of gestation [4]. This definition does not include pregnancies that are recorded as ending in stillbirth (fetal death at 22 weeks or later and before complete expulsion or extraction of the fetus). The strongest indication of a link with maternal reproductive history is based on data from epidemiological studies on neural tube defects [6, 34]. Gravidity has also emerged to be potentially related to Down syndrome, regardless of maternal age [14]. As for CHD, no consensus has been reached, with studies showing both positive and negative associations with gravidity. Both biological and psychosocial interpretations can be proposed, such as maternal stress, maternal uterus condition, and serum levels of estradiol [3, 12, 36, 53].

An increasingly greater number of studies have focused on the association between maternal reproductive history and CHDs; however, the results have been ambiguous, possibly because of inadequate sample sizes. Therefore, we conducted a meta-analysis to quantitatively assess the relationship between the maternal history of abortions, gravidity, and the newborn's risk of CHDs, using 36,582 individuals with 10,132 cases.

Methods

Literature Search

To identify relevant epidemiological studies, a computerized literature search was conducted in MEDLINE and EMBASE from their inception to April 14, 2014, by two investigators (Feng and Yu). We searched relevant studies using the following strategy: (risk factor OR reproductive factor OR history of pregnancy OR reproductive history OR abortion OR miscarriage OR gravidity) AND (congenital heart defect OR heart abnormality OR malformation of heart OR cardiovascular abnormality). Additionally, we conducted a broader search on environmental teratogens and CHDs, and checked the relevant references and review articles so as to identify information from other related studies. We followed the standards of quality for conducting and reporting meta-analyses [41].

Eligibility Criteria

We selected articles that (1) were original epidemiologic studies, (2) examined the association between maternal history of prior pregnancies and abortions and CHDs overall or any one of the CHD subtypes in infants, (3) were published in the English language, (4) reported ORs (i.e., risk ratios or odds ratios) and associated 95 % confidence intervals (CIs) or standard errors or data necessary to recalculate these factors, and (5) defined CHDs or one of the CHD subtypes as an outcome. Articles that reported results from more than one population were considered as separate studies. Since some articles assessed the same link based on data of the same individuals, we used those with a greater number of participants and with the same number of participants. Articles containing more detailed analytic information were also selected.

Data Extraction

Two reviewers (Feng and Yu) working independently extracted data. Studies meeting the inclusion criteria were reviewed to retrieve information of interest including study characteristics (i.e., authors, year of publication, geographic region, periods of data collection, study design, population studied, exposure and outcome assessment, number of cases, number of non-cases, the association measure, point estimates with their corresponding 95 % CIs, and any adjustment/stratification/matching of variables). When no adjusted estimates were available, we extracted the crude estimate. If no estimate was provided in a given study by standard equations, we recalculated odds ratios and 95 % CI from the raw data.

To assess study quality, we used a 9-star system on the basis of the Newcastle-Ottawa Scale [50]. The highest score was 9, and we defined a high-quality study as having quality scores greater than or equal to 7.

Statistical Analysis

In studies without appropriate measurement of associations, aggregated raw data, if available (ignoring matched designs, where necessary), were used for estimating unadjusted associations. For the dose–response analysis, which considers gravidity and the number of prior abortions as continuous variables, the method proposed by Greenland and colleagues [18] and Orsini and colleagues [29] was used to calculate study-specific slopes (linear trends) and 95 % CIs. For studies that reported the duration by ranges, we used the midpoint by calculating the average of the lower and upper bounds. When the highest category was open-ended, we took the length of the open-ended interval to be the same as that of the immediately previous category interval. When the lowest category did not have a lower bound, we considered the lower bound as zero. We presented the dose–response results in forest plots on the basis of each single increment in number of pregnancies.

Cochran Q and I^2 statistics were used to test for heterogeneity across studies [21]. If there was any evidence of heterogeneity ($P < 0.05$ or $I^2 \geqq 50$ %), the random-effects model was used, which provided a more appropriate

summary effect estimate among heterogeneous study-specific estimates. If the study showed no evidence of heterogeneity, the fixed-effects analysis was used, applying inverse variance weighting to calculate summary OR estimates [52].

Publication bias was assessed by visual inspection of a funnel plot for asymmetry, using both Egger linear regression [15] and Begg rank correlation [2] methods. Significant statistical publication bias was defined as a P value of <0.05 for the two tests. All statistical analyses were performed with STATA (version 11.0; StataCorp, College Station, TX, USA).

Results

Study Characteristics

The search strategy generated 1,599 citations, 18 of which were selected for inclusion in the meta-analysis. The 18 studies included 10,132 incident cases [1, 5, 7, 10, 19, 25–28, 33, 38–40, 44, 46, 47, 49, 51] (Fig. 1). All of the studies were published from 1989 to 2014. There were 17 case–control studies and one nested case–control study [28]. Among these studies, ten studies evaluated the association between gravidity and CHD risk, seven of which assessed the association of maternal gravidity number with CHD risk (Table 1). Eleven studies investigated the association of prior abortion with CHD risk, four of which examined the association of abortion number with CHD risk in offspring (Table 2). As shown, seven studies were conducted in the United States, nine in Europe, and two in Asia. Two used hospital-based controls [25, 38]. The quality of included studies, as assessed using the Newcastle–Ottawa quality assessment scales, is shown in Supplementary Table S1.

Gravidity

Ten studies investigated the association between maternal gravidity and a newborn's risk of CHD. The summary OR for the ever pregnant versus nulligravidity was 1.18 (95 % CI 1.03–1.34), with moderate heterogeneity ($Q = 23.60$; $P = 0.005$; $I^2 = 61.9$ %; Fig. 2). There was no indication of publication bias with the Begg test ($P = 0.592$) and Egger test ($P = 0.630$), or by visual inspection of the funnel plot (data not shown). In a sensitivity analysis, we sequentially excluded one study at a time and reanalyzed the data. The ten study-specific ORs of the ever versus nulligravidity ranged from a low of 1.14 (95 % CI

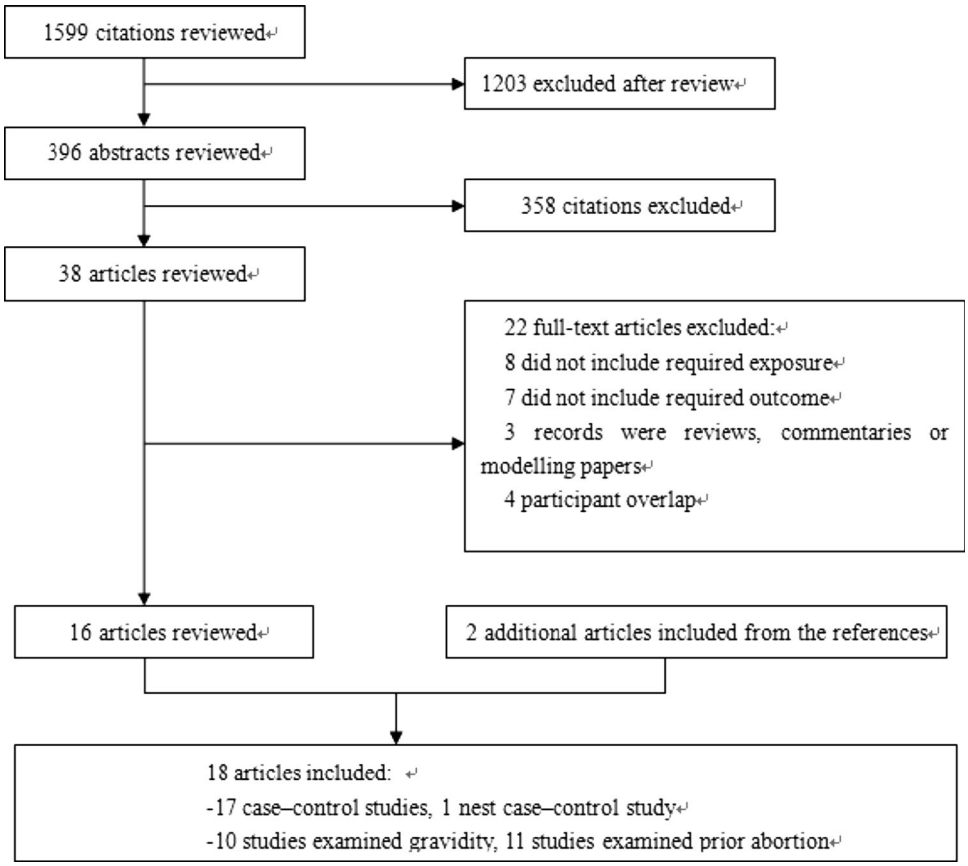

Fig. 1 Study selection procedures for a meta-analysis of maternal reproductive history and congenital heart defects (CHDs) in offspring

Table 1 Characteristics of studies of maternal gravidity and CHD in offspring

First author, year	Region	Period	Study design	No. of cases/non-cases	Exposure	Outcome	Result (OR/HR and 95 % CI)	
Baardman et al. [1]	Netherlands	1997–2008	Population-based case–control/Eurocat Northern Netherlands(Eurocat NNL)	797/322	Gravidity	CHDs	0.80 (0.60–1.06)	
Boneva et al. [7]	USA	1982–1983	Population-based case–control/Atlanta Birth Defects Case–Control Study (ABDCCS)	998/3,029	Number of gravidity	CHDs	1	1.05 (0.88–1.25)
							2	1.03 (0.83–1.26)
							≥3	1.34 (1.08–1.67)
							Any	1.11 (0.95–1.29)
Grewal et al. [19]	USA	1999–2003	Population-based case–control	323/700	Number of gravidity	CHDs	1	1.21 (0.84–1.74)
							2	1.31 (0.89–1.95)
							≥3	1.51 (1.05–2.18)
							Any	1.34 (0.99–1.81)
Liu et al. [25]	China	2004–2005	Hospital-based case–control	164/328	Gravidity,	CHDs	2.68 (1.44–4.97)	
Materna-Kiryluk et al. [28]	Poland	2005–2006	Nested case–control/Polish Registry of Congenital Malformations (PRCM)	1,673/2,068	Number of gravidity	CHDs	1	1.06 (0.86–1.31)
							2	1.03 (0.74–1.43)
							3	2.49 (1.63–3.79)
							Any	1.22 (1.09–1.36)
Stoll et al. [40]	France	1979–1986	Population-based case–control	801/801	Number of gravidity	CHDs	1	0.91 (0.73–1.15)
							≥2	1.13 (0.88–1.46)
							Any	1.00 (0.82–1.22)
Vereczkey et al. [46]	Hungary		Population-based case–control/Hungarian Case–Control Surveillance of Congenital Abnormalities	302/38,151	Number of gravidity	LSOD	1	1.28 (0.98–1.68)
							≥2	1.70 (1.28–2.26)
							Any	1.44 (1.14–1.84)
Vereczkey et al. [47]	Hungary	1980–1986	Population-based case–control/Hungarian Case–Control Surveillance of Congenital Abnormalities	77/38,151	Number of gravidity	CAVC	1	1.03 (0.59–1.80)
							≥2	1.95 (1.14–3.32)
							Any	1.38 (0.87–2.21)
Wasserman et al. [49]	USA	1987–1988	Population-based case–control/California Birth Defects Monitoring Program	207/481	Number of gravidity	CTD	1	1.15 (0.72–1.84)
							2	1.51 (0.95–2.40)
							≥3	1.39 (0.86–2.23)
							Any	1.33 (0.91–1.97)
Williams et al. [51]	USA	1968–1980	Population-based case–control/Atlanta Birth Defects Case–Control Study (ABDCCS)	122/3,029	Gravidity	VSD	0.90 (0.62–1.31)	

CC case–control study, *CHDs* congenital heart defects, *VSD* ventriculap septal defect, *ASD* atrial septal defect, *CTD* conotruncal heart defects, *TOF* tetralogy of Fallot, *TGA* D-transposition of the great arteries, *HLHS* hypoplastic left heart syndrome, *COA* coarctation of the aorta, *AVSD* atrioventricular septal defect, *LOSD* left-sided obstructive defects

Table 2 Characteristics of studies of abortion in the preceding pregnancies and CHD in offspring

First author, year	Region	Period	Study design/Source of cases	No. of cases/non-cases	Exposure	Outcome	Result (OR/HR and 95 % CI)	
Bianca and Ettore [5]	Italy	1991–2000	Population-based case–control/ Sicilian Registry of Congenital Malformation	38/2,000	Number of spontaneous abortion	HLHS	1	0.63 (0.19–2.07)
							2	0.67 (0.09–4.98)
							≥3	80.42 (12.98–498.41)
							Any	1.11 (0.49–2.54)
Boneva et al. [7]	USA	1982–1983	Population-based case–control/Atlanta Birth Defects Case–Control Study (ABDCCS)	998/3,029	Number of spontaneous abortion	CHDs	1	1.29 (1.05–1.59)
							2	1.62 (1.05–2.50)
							3	1.60 (0.68–3.75)
							≥4	1.78 (0.59–5.31)
							Any	1.36 (1.13–1.64)
Cedergren et al. [10]	Sweden	1982–1996	Population-based case–control/Child Cardiology Register	269/524	Number of spontaneous abortion	CHDs	1	1.26 (0.83–1.91)
							2	1.17 (0.51–2.54)
							≥3	1.02 (0.22–3.86)
							Any	1.23 (0.85–1.76)
					Number of induced abortion		1	1.14 (0.72–1.77)
							2	1.08 (0.32–3.25)
							Any	1.13 (0.74–1.71)
Liu et al. [25]	China	2004–2005	Hospital-based case–control	164/328	History of spontaneous abortion	CHDs	3.06 (1.19–7.87)	
Loffredo et al. [26]	USA	1981–1989	Population-based case–control/ Baltimore-Washington Infant Study	1,250/3,568	History of spontaneous abortion	CHDs	1.23 (1.05–1.44)	
Long et al. [27]	USA	1999–2004	Population-based case–control/Texas Birth Defects Registry (TBDR)	1,045/5,225	History of spontaneous abortion	TA	1.29 (0.77–2.17)	
						TGA	0.82 (0.64–1.06)	
						TOF	1.08 (0.87–1.33)	
Materna-Kiryluk et al. [28]	Poland	2005–2006	Nested case–control/Polish Registry of Congenital Malformations (PRCM)	1,673/2,068	History of spontaneous abortion	CHDs	1.13 (0.98–1.31)	
Pradat [33]	Sweden	1981–1986	Population-based case–control/ Registry of Cardiology and The Child Cardiology Registry	1,324/2,648	Number of spontaneous abortion	CHDs	1	1.22 (0.97–1.53)
							2	2.06 (1.29–3.29)
							3	2.31 (0.97–5.50)
							≥4	4 (0.85–24/7)
							Any	1.15 (0.92–1.45)
					History of induced abortion		1.22 (0.97–1.53)	
Sheiner et al. [33]	Israel	1980–1993	Hospital-based case–control	99/103	Number of induced abortion	CHDs	3.2 (1.6–6.7)	

Table 2 continued

First author, year	Region	Period	Study design/Source of cases	No. of cases/non-cases	Exposure	Outcome	Result (OR/HR and 95 % CI)
Steinberger et al. [39]	USA	1981–1989	Population-based case–control/ Baltimore-Washington Infant Study (BWIS)	237/3,572	History of spontaneous abortion	Single ventricle	1.10 (0.3–3.8)
					History of induced abortions		3.60 (1.4–9.4)
Tikkanen and Heinonen [44]	Finland	1982–1983	Population-based case–control/ Finnish Register of Congenital Malformations or the Children's Cardiac Register	406/756	History of spontaneous abortion	CHDs	2.7 (1.4–5.3)
					History of induced abortions		1.1 (0.8–1.6)

CC case–control study, *CHDs* congenital heart defects, *VSD* ventriculap septal defect, *ASD* atrial septal defect, *CTD* conotruncal heart defects, *TOF* tetralogy of Fallot, *TGA* D-transposition of the great arteries, *HLHS* hypoplastic left heart syndrome, *COA* coarctation of the aorta, *AVSD* atrioventricular septal defect, *LOSD* left-sided obstructive defects

1.02–1.28; $Q = 16.59$; $P = 0.035$; $I^2 = 51.8$ %) after omission of the study by Liu and colleagues [30] to a high of 1.22 (95 % CI 1.08–1.37; $Q = 16.40$; $P = 0.037$; $I^2 = 51.2$ %) after omission of the study by Baardman and colleagues. We further created a Galbraith plot to graphically assess the sources of heterogeneity (Supplementary Figure S1). A total of two studies were identified as the main sources of heterogeneity [1, 25]. After the outlier studies were excluded, the heterogeneity was effectively removed ($Q = 9.78$; $P = 0.201$; $I^2 = 28.5$ %), while the corresponding pooled ORs were not materially altered in all comparisons (OR = 1.18, 95 % CI 1.08–1.20).

Seven studies were included in the dose–response analysis. Infants of mothers with no prior pregnancies (primigravida) were used as a reference group. The summary OR for each increment in number of pregnancies was 1.13 (95 % CI 1.08–1.18), with no statistically significant heterogeneity ($Q = 10.43$; $P = 0.108$; $I^2 = 42.5$ %; Fig. 3). Publication bias was not evident from the Begg test ($P = 0.368$), and no asymmetry was observed in the funnel plots.

Prior Abortion

Figure 4 shows the forest plot of the association between prior maternal abortion and the newborn's risk of CHD. When all studies of CHD and prior abortion were combined, a history of abortion was associated with a 24 % higher risk of CHD (OR = 1.24, 95 % CI 1.11–1.38). Moderate heterogeneity was detected ($Q = 29.84$, $P = 0.019$, $I^2 = 46.4$ %), with no publication bias (Begg test: $P = 0.108$). When stratified by abortion category, there was an 18 % increment in CHD risk with a history of spontaneous abortion (OR = 1.18, 95 % CI 1.07–1.31), whereas an increase in risk of 58 % was found for a history of induced abortion (OR = 1.58, 95 % CI 1.12–2.22). In a sensitivity analysis, the 11 study-specific ORs for a history of abortion ranged from a low of 1.21 (95 % CI 1.09–1.33; $Q = 23.27$; $P = 0.079$; $I^2 = 35.3$ %) after omission of the study by Sheiner and colleagues [38] to a high of 1.29 (95 % CI, 1.15–1.45; $Q = 23.43$; $P = 0.037$; $I^2 = 44.5$ %) after omission of the study by Long and colleagues [27].

Four studies were included in the maternal abortion dose–response analysis. The summary OR for each increment of one abortion was 1.28 (95 % CI 1.18–1.40), with no statistically significant heterogeneity ($Q = 6.66$; $P = 0.084$; $I^2 = 54.9$ %) or publication bias (Begg test: $P = 0.734$; Egger test: $P = 0.450$) (Fig. 5).

Discussion

To the best of our knowledge, this is the first quantitative meta-analysis evaluating the association between maternal reproductive history and the newborn's risk of CHD.

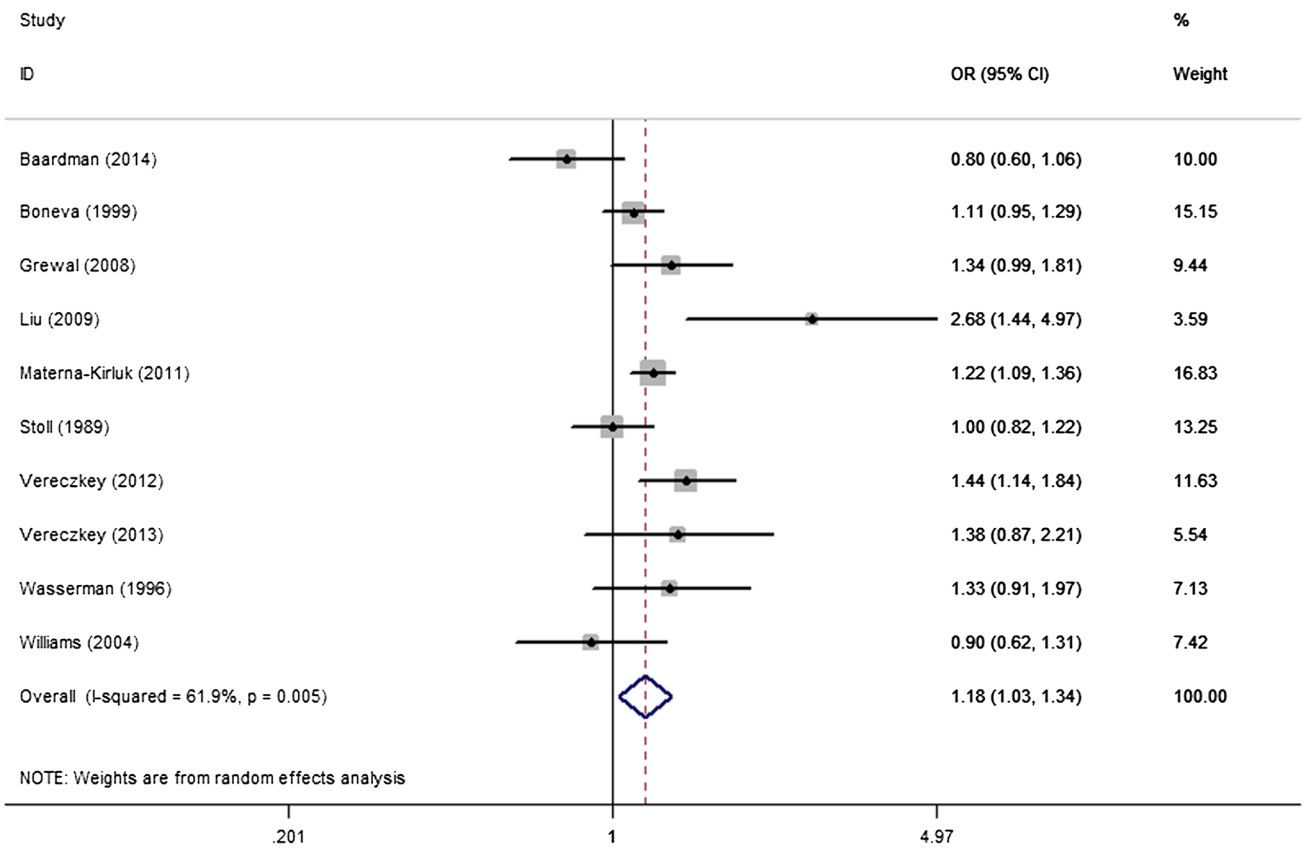

Fig. 2 Forest plot showing the ORs and 95 % CIs for studies investigating the association between gravidity (ever versus nulligravidity) and congenital heart defects in offspring

Overall, this meta-analysis provided a robust estimate of the positive association between gravidity, history of prior abortion, and the risk of CHD in offspring. The summary OR for the ever versus nulligravidity was 1.18 (95 % CI 1.03–1.34). Meanwhile, in the dose–response meta-analysis, we found that the risk of CHDs increased by 15 % for each increment of one pregnancy. On average, women with a history of abortion were at a 24 % higher risk of CHD in offspring. For a history of spontaneous and induced abortion, increases in risk of 18 and 58 %, respectively, were found.

Although the specific biological mechanism underlying maternal gravidity and the risk of CHD remains unclear, it has been suggested that nutrient depletion is more likely to occur among mothers who had more live fetuses than those who never delivered. Folic acid is one of the most important vitamins, and the association between folic acid and birth defects has been widely studied. It has been confirmed that lack of folic acid can cause severe congenital malformation [8], especially CHDs [35] and neural tube defects [13]. Additionally, mothers who had more pregnancies were more likely to have a shorter interpregnancy interval, which increases the risk of major congenital malformation, including CHD [20]. What is more, young children can carry respiratory viruses in the household, which increases the risk of in utero embryo exposure to virus, especially rubella, which has been known for more than half a century to increase the risk of CHD [17, 42]. Besides, CHD risk might be explained by more pregnancies, which may change the intrauterine environment and affect embryonic development, leading eventually to birth defects. Except for biological interpretations, psychosocial explanations have also been proposed. Multigravidity can increase family burden and cause mental stress to parents. Moreover, Zhu et al. [53] found that exposure of mothers to stress during pregnancy might increase the risk of CHD in the offspring. As for a history of prior abortion, several etiological arguments support a common mechanistic pathway for the risk of CHD among newborns. A uterine factor might lead to deficient implantation, particularly when the fertilized ovum is abnormal. Different types of abortion might result in some residual effect that might influence the fetus [37]. Furthermore, several chronic maternal diseases are associated with an increased risk of abortion, including coagulation dysfunction [31], hyperglycemia [24], and insulin

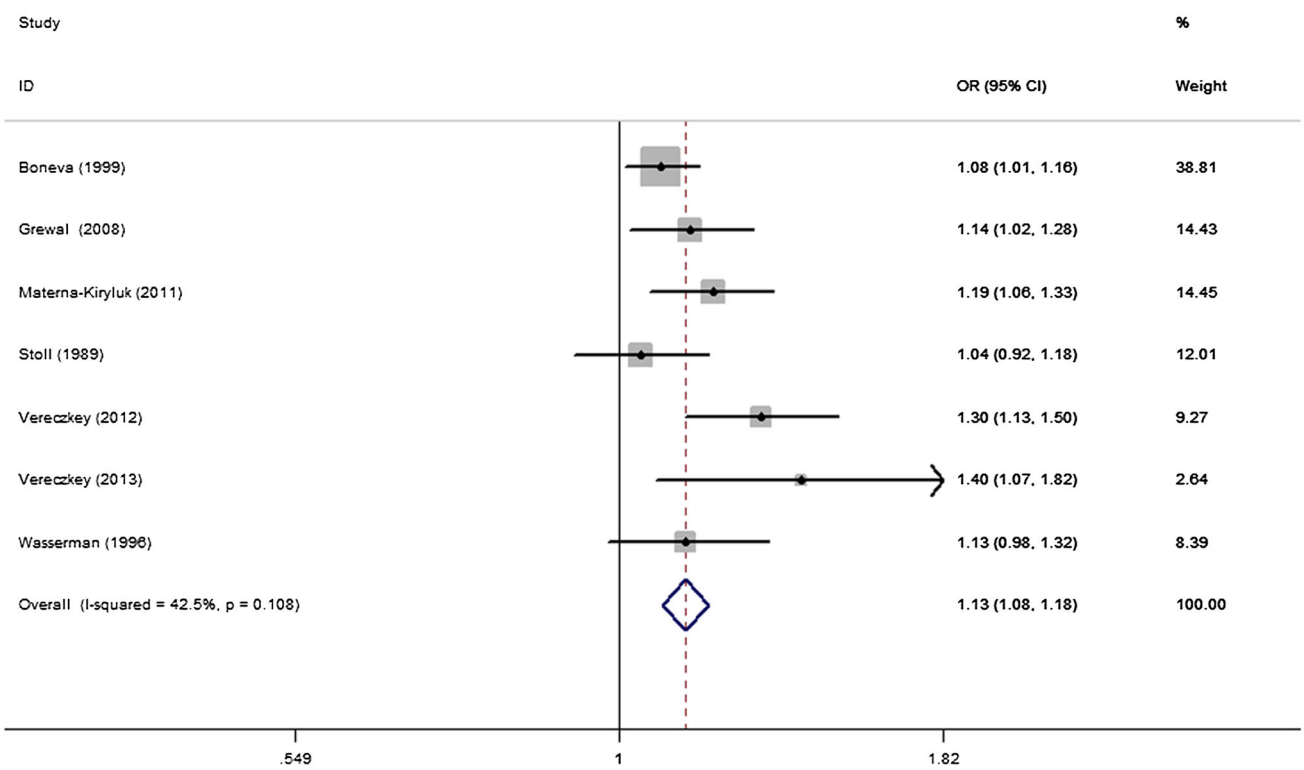

Fig. 3 Forest plot showing the ORs and 95 % CIs for studies investigating the association between gravidity number (number of pregnancies) and congenital heart defects in offspring

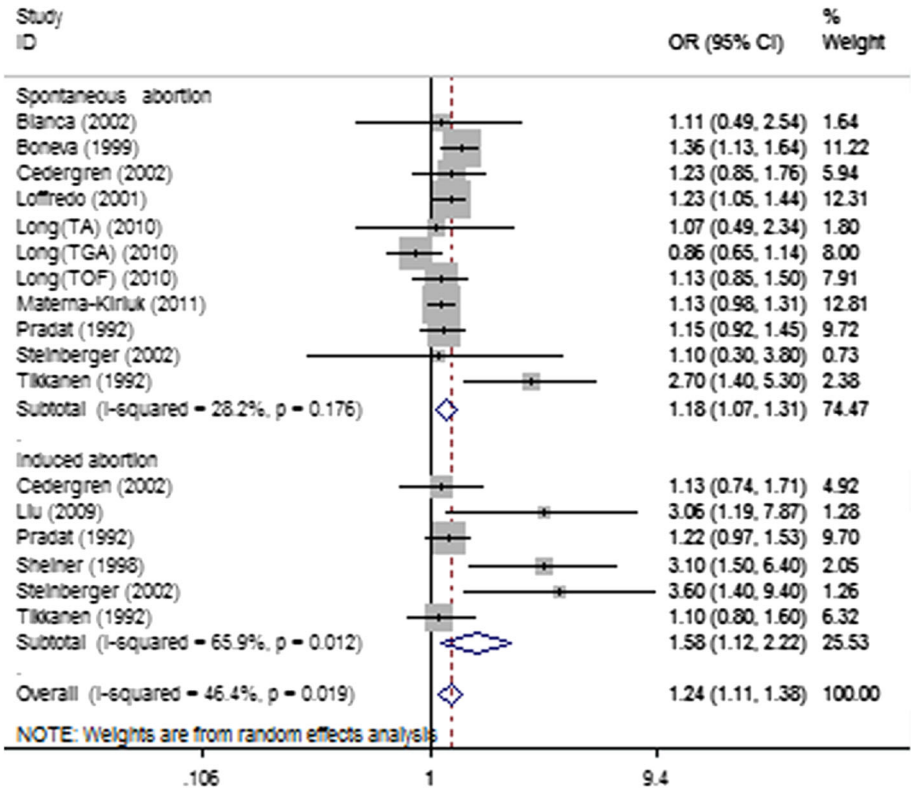

Fig. 4 Forest plot showing the ORs and 95 % CIs for studies investigating the association between a history of abortion and congenital heart defects in offspring

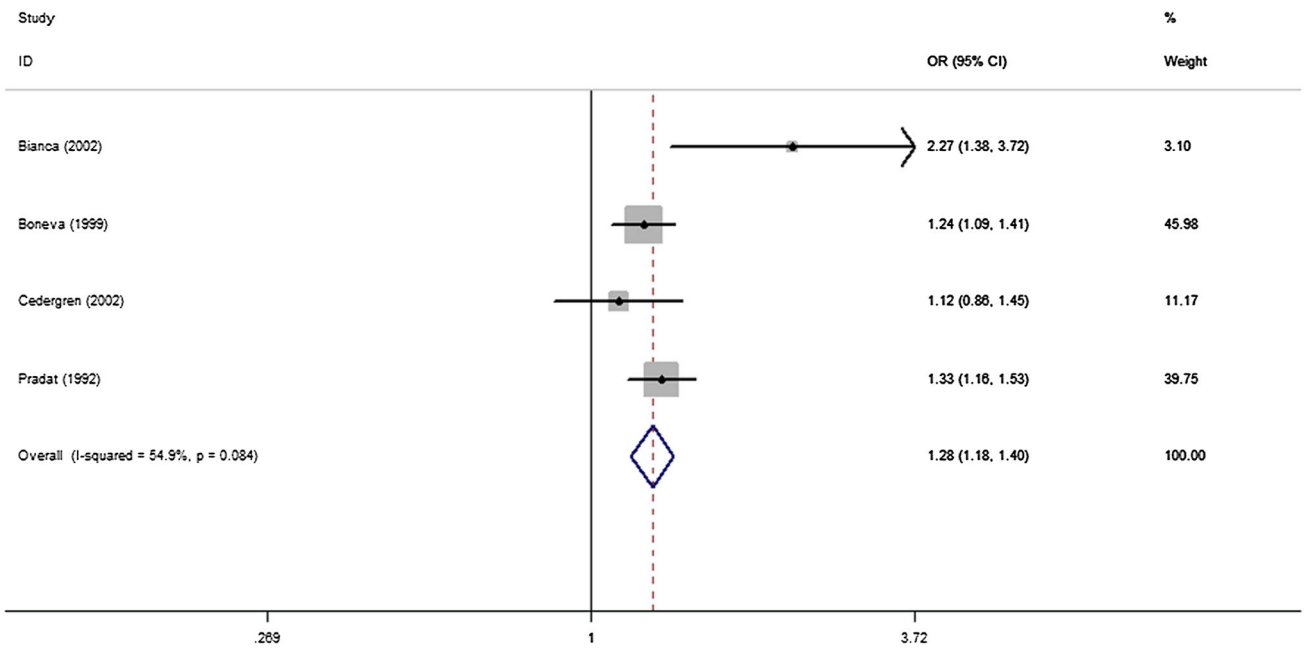

Fig. 5 Forest plot showing the ORs and 95 % CIs for studies investigating the association between abortion number (each prior abortion) and congenital heart defects in offspring

resistance [11, 43]. According to a recent meta-analysis, there is an increase in the likelihood of CHD among offspring of diabetic mothers [9].

The limitations of our study include the use of raw data from case–control studies, which are susceptible to selection and information biases (17 case–control studies and one nested case–control study). Another possible limitation is that our meta-analysis was limited to studies published in English, and thus we may have missed data from studies performed in other languages. Because we lacked a large dataset, we did not conduct subgroup analyses of CHD subtypes. Different CHD subtypes have different etiologies, and maternal reproductive history may be not associated with all subtypes. Thus, our general conclusions must take these limitations into consideration. Future meta-analyses should include more high-quality studies.

There are several important strengths to our study. First, to our knowledge, this is the first meta-analysis to report an association between maternal reproductive history and newborn CHDs. Our study included 10,132 cases, which could have sufficient statistical power to investigate the potential association between maternal reproductive history and the risk of CHD. Another strength of our study is that although heterogeneity exists in our meta-analysis, we conducted a number of sensitivity and Galbraith plot analyses, and the results were stable.

In summary, this study provides a robust estimate that increased maternal gravidity was positively associated with a risk of CHD in offspring. Our results demonstrate a positive association of any history of abortion with an increased risk of CHD. However, more prospective studies, particularly in developing countries, are needed to further investigate the association, especially with regard to the different subtypes of CHDs.

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