

Review Article

History of infertility relates to increased risk of gestational diabetes mellitus: a meta-analysis

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Abstract: Objective: History of infertility may be related to the development of gestational diabetes mellitus (GDM). However, studies investigating the relationship between history of infertility and GDM have yielded inconsistent findings. We performed a meta-analysis with all studies currently available to precisely estimate the association between history of infertility and GDM risk. Methods: The PubMed, Web of Science, Embase, China National Knowledge Infrastructure (CNKI), and Wanfang databases were searched for relevant articles published up to Sep. 1st, 2016 without language restriction. Relative ratios (RRs) with 95% confidence intervals (95% CIs) were calculated using STATA 12.0 software to evaluate the association of infertility and GDM risk. Results: Ten studies involving 430,715 subjects were included into our study. Overall, history of infertility was related to significantly increased risk of GDM (RR=1.90, 95% CI 1.50-2.40, P<0.001). Subgroup analyses by ethnicity and treatment of infertility further confirmed the findings. Sensitivity analysis showed that no single study materially influenced the pooled results in this meta-analysis. Conclusion: History of infertility may be a risk factor of GDM, particularly in patients receiving treatment for infertility.

Keywords: Infertility, gestational diabetes mellitus, meta-analysis

Introduction

Gestational diabetes mellitus (GDM) is one of the most common pregnancy complications. GDM is defined by the American Diabetes Association as blood glucose concentrations greater than ≥ 5.8 mmol/L during pregnancy and is thought to affect approximately 10 percent of pregnancies worldwide [1, 2]. With the escalating prevalence of overweight and obesity due to increased diet and reduced exercise among women at reproductive age, the incidence of GDM increases significantly [3, 4]. It has been suggested that GDM possesses a small but potentially important long-term metabolic risk for both mother and offspring [5-10]. Many factors including family history of diabetes, older maternal age at pregnancy, pre-pregnancy overweight and obesity, poor diet and low physical activity are responsible for an elevated risk of GDM [11-13].

Infertility is defined as absence of conception with an attempt to pregnancy during more than 12 months [14]. There are approximately 12%-30% of couples suffering the trouble of infertility in the world [15]. Infertility may be attributed to diverse factors involving but not restricted to polycystic ovary syndrome (PCOS), endometriosis, tubal blockage and ovulatory disorders [16-19]. Since many obesity-related metabolic disturbances are similarly involved in infertility and GDM, they may possibly share part of the pathogenesis, such as insulin resistance and inflammation. During the past few years, a number of studies have investigated the relationship between history of infertility and GDM risk [20-29]. However, they have provided conflicting and inconclusive findings, which may be attributed to single study with insufficient statistical power caused by relative small sample size, different ethnicity and study design. Meta-analysis can better estimate the possible asso-

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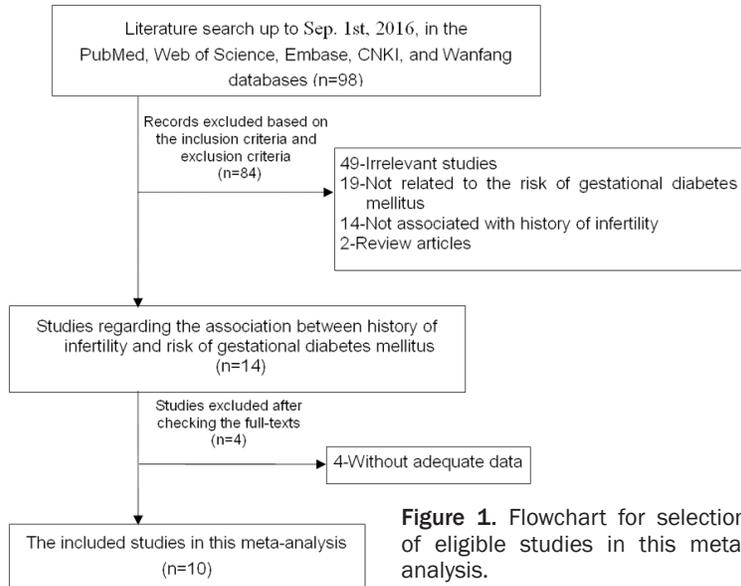


Figure 1. Flowchart for selection of eligible studies in this meta-analysis.

ciation by pooling all available data. The aim of this study is to shed some light on those findings and provide precise evaluation for the association between history of infertility and the risk of GDM.

Materials and methods

Search strategy

To identify studies on the association between history of infertility and risk of GDM, a systemic literature search of all currently available studies in PubMed, Web of Science, Embase, China National Knowledge Infrastructure (CNKI), and Wanfang databases up to Sep. 1st, 2016 was conducted. The search terms were as follows: infertility, reproductive sterility, dysgenesis, subfertility, or assisted reproductive technique; and GDM, gestational diabetes, or pregnancy-induced diabetes; and risk.

Inclusion criteria

Studies included into this meta-analysis should conform to the following inclusion criteria: (1) publications on the association between history of infertility and risk of GDM; (2) case-control studies or cohort or cross-sectional studies; (3) sufficient data for calculating relative risks (RRs) with 95% confidence intervals (CIs). For the duplications of previous publications, only the study with the largest sample size or the most recent one was included into this meta-analysis.

Exclusion criteria

Exclusion criteria were as follows: (1) reviews; (2) non case-control or non-cohort or non cross-sectional studies; (3) studies without available data for meta-analysis; (4) studies with duplicated data.

Data extraction

Two investigators extracted data independently from all available articles according to the inclusion and exclusion criteria, and discrepancies were solved by discussion. We didn't contact with any author for information about all studies included into our study. The following

data were extracted: the first author, year of publication, country of subjects, ethnicity, study design, and RR value with 95% CIs.

Statistical analysis

The strength for relationship between history of infertility and risk of GDM was estimated by calculating the pooled RRs with 95% CIs by using STATA 12.0 software. To assess the possible heterogeneity between all included studies, Cochran's chi-square-based Q statistic test and I^2 test were used [30, 31]. According to the results of heterogeneity analysis, the random-effects model (the Der Simonian and Laird method) or the fixed-effects model (the Mantel-Haenszel method) was selectively used to assess the pooled RRs. Sensitivity analysis by omission of single study was conducted to confirm the reliability and stability of the pooled results. Publication bias was evaluated by Begg's funnel plot and Egger's test [32, 33]. A two tailed P value less than 0.05 was considered statistically significant.

Results

Literature search and characteristics of all eligible studies

Ninety-eight articles (seventy-nine written in English and nineteen written in Chinese) were identified after a comprehensive literature search in PubMed, Web of Science, Embase, CNKI, and Wanfang databases. After reviewing the titles and abstracts, eighty-four papers

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Table 1. Characteristics of all included studies

First author	Year	Study design	Ethnicity	No. of Subjects	Incident	Adjusted or matching factors
Holst S	2016	Population-based cohort study	Caucasians	372677	History of infertility	Year of delivery, maternal age, parity, parental history of diabetes, educational level, prepregnancy BMI, and maternal smoking in pregnancy
Zhang J	2015	Prospective cohort study	Asians	3216	Treatment for infertility	Maternal age, ethnicity, body mass index
Ashrafi M	2014	Cross-sectional study	Caucasians	702	Treatment for infertility	Age, parity and hypothyroidism
Ashrafi M	2014	Cross-sectional study	Caucasians	360	Treatment for infertility	Age, pre-pregnancy BMI and weight gain in pregnancy
Tobias DK	2013	Prospective cohort study	Mixed	40773	History of infertility	Age, prepregnancy body mass index, family history of diabetes, race/ethnicity and marital status
Camarano L	2012	Retrospective cohort study	Caucasians	1991	History of infertility	Age, pre-pregnancy BMI
Reyes-Munoz E	2012	Retrospective cohort study	Caucasians	104	History of infertility	Age, pregestational BMI and parity
Bhat M	2010	Case-control study	Asians	600	Treatment for infertility	NR
Yasmin H	2006	Retrospective cohort study	Caucasians	105	History of infertility	NR
Berkowitz GS	1992	Retrospective cohort study	Mixed	10187	History of infertility	Age, prepregnancy weight, and a family history of diabetes

NR, not reported.

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Table 2. Meta-analysis results

Contrasts	Relative Ratio		I ² (%)	P _H [†]
	RR [95% CI]*	P _{RR}		
Total studies	1.90 [1.50, 2.40]	<0.001	86.8	<0.001
Subgroup analysis by ethnicity				
Asians	2.58 [1.11, 5.98]	0.028	84.5	0.011
Caucasians	2.06 [1.23, 3.45]	0.006	90.7	<0.001
Subgroup analysis by treatment for infertility				
	3.17 [1.67, 6.04]	<0.001	88.0	<0.001

*RR, Relative Ratio; 95% CI, 95% Confidence Interval; †P_H, P value of heterogeneity analysis.

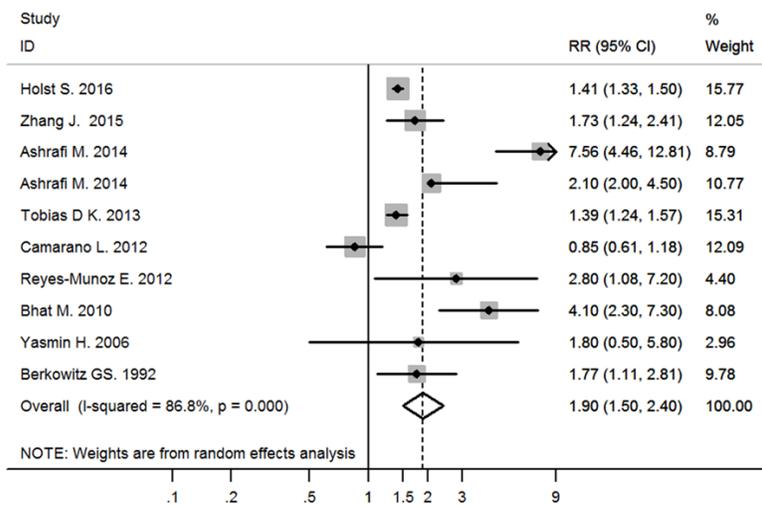


Figure 2. Forest plot for history of infertility and GDM risk.

were excluded for irrelevance or duplication. Fourteen articles were reviewed carefully, of which four with inadequate data were omitted. Overall, ten publications involving 430,715 female subjects were retrieved according to the inclusion criteria [20-29]. Details for the inclusion of all eligible studies were presented in **Figure 1**. The characteristics of all included articles were summarized in **Table 1**.

There were seven cohort studies, two cross-section studies and one case-control study. Among the ten independent studies, six were conducted in Caucasians, two were in Asians and the other two were based on mixed ethnicity. The association between infertility and GDM was investigated in all ten studies. Subjects in four studies had a history of infertility and received treatment for infertility, such as assisted reproductive technique.

History of infertility as a risk factor of GDM

As suggested by overall analysis of all involved studies, history of infertility was related to

significantly increased risk of GDM (RR=1.90, 95% CI 1.50-2.40, P<0.001) (**Table 2; Figure 2**). However, significant between-study heterogeneity was found among all included studies (I²=86.8%, P<0.001) (**Table 2; Figure 2**).

Stratified analysis by ethnicity indicated that elevated risk of GDM was observed to be associated with history of infertility in Asians (RR=2.58, 95% CI 1.11-5.98, P=0.028; I²=84.5%, P=0.011) (**Table 2; Figure 3**), and significant relationship between history of infertility and GDM risk was determined in the

Caucasians (RR=2.06, 95% CI 1.23-3.45, P=0.006; I²=90.7%, P<0.001) (**Table 2; Figure 3**).

Subgroup analysis in studies regarding the treatment for infertility showed that history of infertility exerted risk effect on the occurrence of GDM (RR=3.17, 95% CI 1.67-6.04, P<0.001; I²=88.0%, P<0.001) (**Table 2; Figure 4**).

Test of heterogeneity and publication bias

As is shown in **Table 2**, significant between-study heterogeneity was found among all included studies. Therefore, the random-effect model was used to evaluate the association between history of infertility and GDM risk. The source of heterogeneity could not be determined, although subgroup analysis and sensitivity analysis were carried out.

Begg's funnel plots for all contrasts seemed symmetrical, indicating no potential publication bias in our study. In addition, the quantitative

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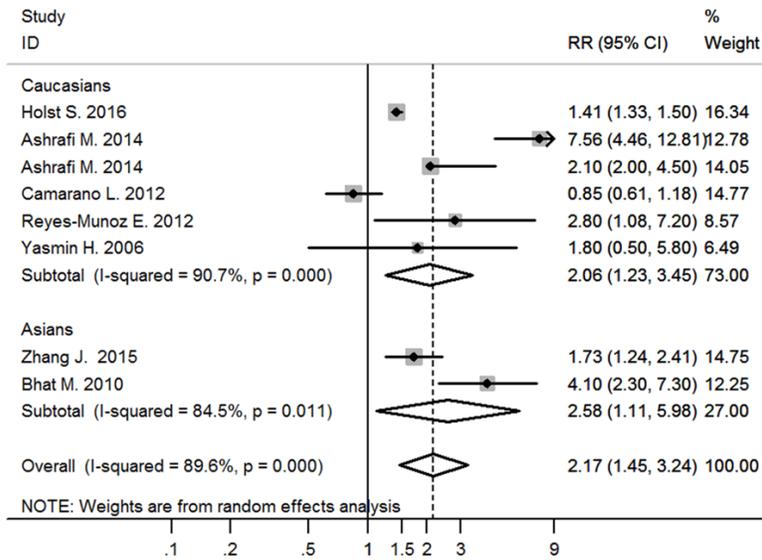


Figure 3. Association between history of infertility and GDM risk in Asians and Caucasians.

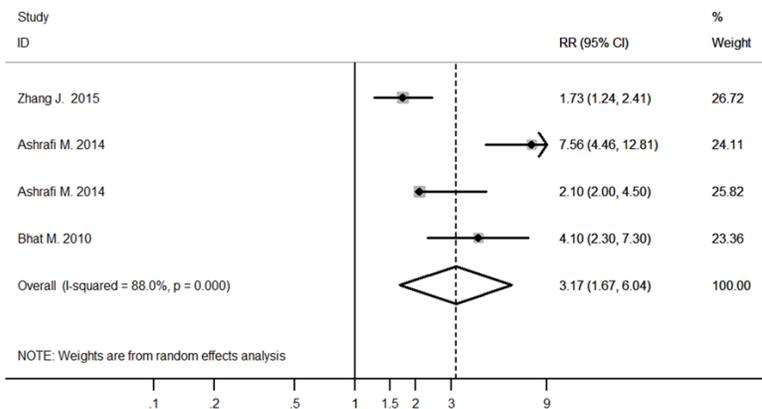


Figure 4. Association between history of infertility and GDM risk in patients receiving treatment for infertility.

evaluation by Egger's test ($P=0.111$) further showed there was no publication bias risk in this meta-analysis (**Figure 5**).

Discussion

The present meta-analysis of ten independent studies shows the evidence that history of infertility confers risk effect on the development of GDM, especially in Asians and patients under treatment for infertility. Accordingly, history of infertility may be a risk factor for GDM.

Infertility is a common disease among women at reproductive age, extraordinary young females. Causes of infertility can be classified into

two variants: social-psychological factors such as demographic factors, lifestyle, environmental factors and psychological factors; physiological and pathological factors, such as anatomy, endocrinology and metabolism, infection and endometriosis [34]. Of these factors, metabolism and infection are the emerging pathogenesis for infertility, which makes infertility share the parallel mechanism with many other diseases, such as obesity, cancer, cardiovascular diseases and diabetes mellitus. Previous studies have suggested that history of infertility and infertility treatment may increase the risk of endometrial cancer, breast cancer, atherosclerosis, hypertension and diabetes [35-39].

GDM represents relative beta-cell dysfunction due to insulin resistance in response to the metabolic stress experienced during pregnancy [40]. O'Sullivan reported that 50% of GDM patients would develop diabetes in a follow-up study of 22-28 years [41]. Other studies also revealed that GDM may contribute to increased risk of atherosclerosis, [42, 43] maternal renal disease [44] varying degrees of maternal hyperglycemia and pregnancy-associated diseases. Proper care or treatment during pregnancy may reduce the incidence of GDM or weaken the adverse effect of GDM. Therefore, it is of great significance to predict the occurrence and early diagnose of GDM, and provide appropriate interventions. The frequency of GDM is rising [45]. Many studies have been performed to identify risk factors for GDM. Delivery at older age, body mass index (BMI) >30 kg/m² during pregnancy, previous macrosomic baby weighing ≥ 4.5 kg, previous GDM, family history of diabetes, and ethnicity of high prevalence are indicated as risk factors for GDM. Additionally, history of PCOS, history of chronic hypertension,

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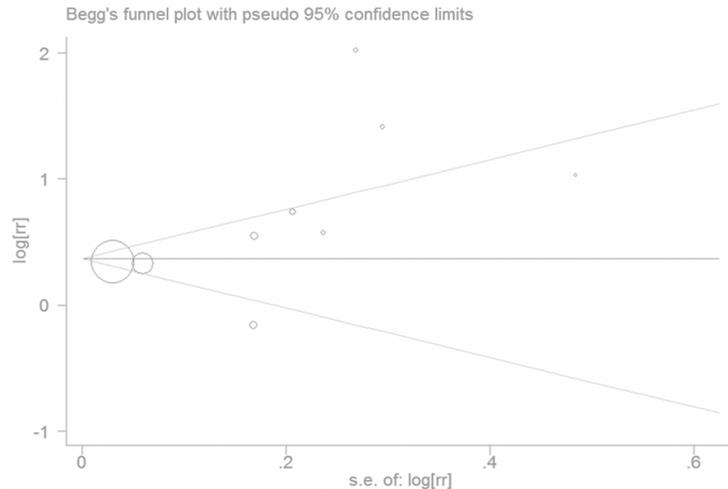


Figure 5. Begg's funnel plot for the evaluation of publication bias risk.

previous stillbirth and glycosuria in current pregnancy are suggested as significant predictors for GDM.

Berkowitz GS et al. firstly assessed the association between history of infertility and GDM, and he found that women with a history of infertility were at an increased risk for GDM. However, Berkowitz GS predicted that the association of GDM risk with infertility may be specific to PCOS [22]. As a verification, the study carried out by Yasmin H et al. suggested that history of infertility itself could be a predictor for prenatal complications [28]. It was well documented that PCOS conferred a high risk to the development of GDM, [46] similar findings were reported by Reyes-Munoz E and the colleagues [26]. PCOS is an important pathogenesis of female infertility and 70% patients with PCOS suffers from infertility. Accordingly, women with a history of infertility and/or PCOS are at increased risk for GDM. Moreover, it has been suggested that women who have experienced the treatment for infertility were at higher risk for GDM [23]. Currently, ten relevant studies have investigated the association between history of infertility and the risk of GDM [20-29]. Findings were inconsistent. There was no significant association between history of infertility and the GDM risk, suggested by the study by Camarano L et al. [24]. On the contrary, an increased risk of GDM related to the infertility history was also demonstrated in some other studies [20-23, 25-29]. Our study suggested significant association between history of infertility and the risk of GDM. The pooled RRs sug-

gested that history of infertility is an independent risk factor of GDM, especially in people experiencing treatment for infertility.

Some limitations must be seriously considered in our meta-analysis. First, only published articles were included. Studies published from Sep. 1st, 2016 up to now were not screened. Second, as mentioned above, the between-study heterogeneity was significant between all included studies, while the source of heterogeneity was not determined. Third, our data was based on unadjusted estimates for lack of sufficient available

information in individual studies. Confounding factors such as age, sex, and so forth, should be considered when assessing the association of infertility history with GDM risk. Last but not the least, future studies investigating the correlation between infertility history and GDM risk should elucidate the influence of PCOS.

In summary, the current meta-analysis suggests that the history of infertility may be a risk factor of GDM, particularly in patients receiving treatment for infertility. However, more studies with high quality are warranted for further elucidation.

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Disclosure of conflict of interest

None.

Authors' contribution

Contributions of all the co-authors are listed as follows: H Wang, Z Wang, J Meng, L Liu and B Chen conceived and designed the study. H Wang, Z Wang, J Meng and X Wang performed the study, J Meng and X Wang searched databases, H Wang and Z Wang assessed the study eligibility and performed data extraction. H Wang, B Chen analyzed the data. H Wang, Z Wang, J Meng, B Chen wrote the manuscript, and L Liu revised the manuscript.

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