Original Article

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Association between maternal diabetes mellitus and the risk of congenital malformations: A meta-analysis of cohort studies

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Summary **Increasing studies suggest that gestational diabetes mellitus (GDM) and pre-gestational diabetes mellitus (PGDM) may be associated with an increased risk of major congenital malformations (MCM) in the offspring. To determine whether GDM or PGDM is associated with an increased risk of congenital malformations, we performed a meta-analysis of cohort studies. We systematically searched the PubMed, Web of Science and Cochrane Library (from January, 1990 to October, 2014) and reviewed the reference lists of included papers to search for additional studies. Meta-analysis tools were used to summarize results. Summary relative risks (RRs) with 95% confidence intervals (CIs) were calculated with random-effects models or fixed-effects models. Study quality was assessed using the Newcastle-Ottawa scale. A total of 21 cohort studies were included in the meta-analysis. Analysis of all studies showed that both PGDM and GDM were associated with an increased risk of MCM (RR = 2.44, 95% CI = 1.92-3.10, I^2 = 78.3%, p = 0.342; RR = 1.11, 95% CI = 1.11-1.27, I^2 = 9.9%, p < 0.001, respectively). There is a slightly higher risk of major congenital malformations in women with GDM than in the reference group. However, this risk is much lower than in women with PGDM. Further large-scale prospective cohort studies are needed to test the effect of PGDM and GDM on specific congenital malformations risk.**

Keywords: Gestational diabetes, pre-gestational diabetes, congenital malformations, meta-analysis

1. Introduction

Women with diabetes in pregnancy can be divided into two groups: women with diabetes diagnosed before pregnancy (pre-gestational diabetes) and women with glucose intolerance diagnosed during pregnancy (gestational diabetes mellitus). Women with diabetes before pregnancy, that is, pre-gestational diabetes mellitus (PGDM), have an increased risk of pregnancy complications (*1-5*), including serious perinatal outcomes such as stillbirth, perinatal mortality, and major congenital malformations. It is reported that in the offspring of women with PGDM, the incidence of cardiovascular abnormalities ranges from 2 to 34 per 1,000 births, central nervous system abnormalities from 1 to 5 per 1,000 births, musculoskeletal abnormalities from 2 to 20 per 1,000 births, genitourinary abnormalities from 2 to 32 per 1,000 births (*6-8*). However, whether the risk of MCH is also increased in gestational diabetes mellitus (GDM) remains inconsistent. Some authors (*8-12*) have reported that GDM is associated with an increased risk of CM in the offspring, while others (*13,14*) have reported a risk comparable with that in the reference group. Still other papers (*7,15-17*) reported that women with gestational diabetes are not at risk for infant malformations. Therefore, this study was designed to perform a meta-analysis of cohort studies to evaluate the association between maternal diabetes mellitus and the risk of congenital malformations in the offspring.

2. Materials and Methods

2.1. *Search strategy*

We systematically conducted a literature search of

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PubMed, Web of Science and Cochrane Library from January 1990 to October 2014, for human studies of maternal diabetes mellitus and the risk of congenital malformations in any language. Our overall search strategy included medical subject heading terms and/or text words: diabetes mellitus (PGDM, pregestational diabetes, pregnancy in diabetes, pregnancy in diabetics, GDM, gestational diabetes mellitus, pregnancy-induced diabetes), complications or outcomes (anomalies, congenital anomalies, malformations, congenital malformations, defects, birth defects, congenital defects). In addition, we reviewed the reference lists of including articles and recent reviews. Two independent investigators screened titles/abstracts according to the following inclusion and exclusion criteria.

2.2. *Inclusion and exclusion criteria*

A study was included in this meta-analysis if it met the following criteria: *i*) the study design was based on cohort studies; *ii*) the study evaluated the association between maternal diabetes mellitus and congenital malformations risk; *iii*) one of the outcomes under study contains congenital malformation; and *iv*) study must contains reference group. Studies were excluded if they only provided a percentage of the incidence of congenital malformation. If the publications were duplicated or shared in more than one study, the most recent publications were included.

2.3. *Data extraction*

Two authors independently extracted the following data from each publication: publication data (author, year of publication and country of population studied), methods of diabetes assessment (self-reported, registration and measuring blood glucose). Number of exposed and unexposed. Disagreements were resolved by discussion, consensus and arbitration by a third author. We evaluated the methodological quality based on the Newcastle–Ottawa Scale (NOS). The NOS contains eight items, categorised into three dimensions including selection, comparability and outcome. We defined NOS scores of 1–3, 4–6, and 7–9 for low, intermediate, and high-quality studies, respectively. And maximum score = 9. Ethical consent for the work was not required.

2.4. *Statistical analysis*

We conducted a meta-analysis of maternal diabetes mellitus and the risk of congenital malformations. Relative risk (RR) was used to estimate the effect sizes. To describe the percentage of total variation across studies attributable to heterogeneity, we used the I^2 statistic (18). A fixed-effect model was used to evaluate the RR and 95% CI if no significant heterogeneity ($p > 0.05$ and $I^2 < 50\%$) existed. Otherwise, a random-effect model was selected. For I^2, a value > 50% was considered to have severe heterogeneity. In an attempt to evaluate the possible publication bias, Begg's test (rank correlation method) (*19*) were used, and a p value of < 0.05 was considered representative of significant statistical publication bias. All statistical analyses were performed with STATA version 11.0 software (StataCorp, College Station, TX).

3. Results

3.1. *Characteristics of the subjects in selected studies*

Detailed search procedures are summarized in Figure 1. The search strategy identified 4,854 references. Two studies (*20,21*) were added through reference lists of including articles searches. After excluding duplicate articles, we reviewed titles and abstracts of all identified studies to exclude those that were clearly irrelevant. Next, the full texts of the remaining articles were examined according to the inclusion and exclusion criteria. We identified 74 relevant publications for detailed evaluation and inclusion in the meta-analysis. After examining these articles in more detail, a further 53 studies were excluded. At the end of this process, 21 studies were included in the meta-analysis (*5,7,8,10-15,20-31*).

Table 1 provides information about the characteristics of the studies included (21, from five continents). The numbers of included women amount to 2,788,521 for the reference group, 34,225 for GDM and 11,210 for PGDM.

3.2. *Study quality*

We assessed study quality using the Newcastle-Ottawa scale. Since the assessment of quality related strongly to the reporting of results, a well conducted study could score poorly if the methods and results were not reported in sufficient detail. Therefore, we reported the assessment in scores. The mean NOS score for the studies was 5.43, which indicated that the study had an intermediate quality (Table 2).

3.3. *Publication bias*

To assess bias across studies, funnel plot asymmetry was checked with Begg's test to identify small study effects for the association between GDM and the risk of congenital malformations ($p = 0.979$, 95% CI = –0.84-0.82), indicating a low probability of publication bias (Figure 2). Begg's test was also used to identify small study effects for the association between PGDM and the risk of congenital malformations ($p = 0.947$, 95% CI = –2.39-2.25), indicating a low probability of publication bias (Figure 3).

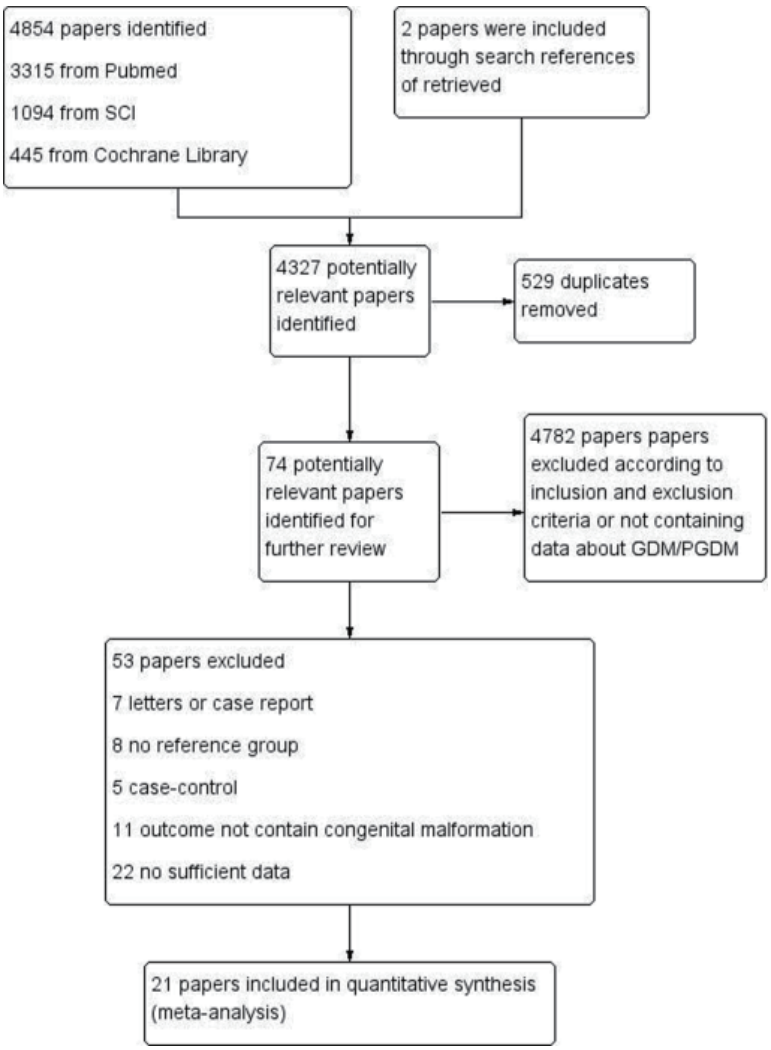

Figure 1. Flow chart on the articles selection process.

Table 1. Characteristics of studies included in the meta-analysis

Author/year	Country	GDM criteria	GDM		PGDM		Reference	
			Events (*n*)	Total (*n*)	Events (*n*)	Total (*n*)	Events (*n*)	Total (*n*)
Hod/1991	Israel	ADA	26	878	8	132	7	380
Janssen/1996	USA	NP	242	8,868	111	1,511	214	8,926
Hod/1996	Israel	ADA	4	250			9	470
Kimmerle/1997	Germany	NP			50	2,402	7,185	595,393
Djelmis/1997	Croatia	WHO (IGT/GDM)	0	94			0	46
Ramachandran1998	India	NDDG	5	211			8	851
Moore/2000	USA	NP	7	506	4	68	299	22,377
Suhonen/2000	Finland	NP			30	709	10	735
Sheffield/2002	USA	NDDG	35	2,277	25	410	2,075	142,509
Abdelgadir/2003	Sudan	WHO (DM)	0	19	3	69	0	50
Savona-Ventura/2003	Malta	OGTT*	4	242	3	47	318	8,547
Bo/2004	Italy	C and C	3	135			10	496
Chico/2005	Spain	C and C/NDDG	7	404			83	5,844
Ricart/2005	Spain	ADA/NDDG	17	819			133	8,451
Sharpe/2005	Australia	OGTT**	405	6,735	96	946	14,257	282,260
Shefali/2006	India	ADA/WHO	2	146	3	79	0	30
Abolfazl/2008	Iran	NP	4	70			3	350
Peticca/2009	Canadian	NDDG	26	2,046	18	891	727	50,914
Fadl/2010	Sweden	OGTT***	242	10,525			22,496	1,249,772
Bell/2012	UK	NP				1,677	7,613	399,472
Vinceti/2014	Italy	NP				2,269	202	10,648

C and C, Carpenter and Coustan; IGT, impaired glucose tolerance; NDDG, National Diabetes Data Group; GDM, gestational diabetes mellitus; PGDM, pregestational diabetes mellitus; ADA, American Diabetes Association; OGTT*, 2 h post-OGTT ≥ 8.6 mmol/L; OGTT**, 2 h post-OGTT ≥ 8.0 mmol/L; OGTT***, 2 h post-OGTT ≥ 9.0 mmol/L; NP, Not Provided.

Table 2. Assessment of study quality

Cohort studies		Quality Assessment Items					
		Representativeness of the cohort	Ascertainment of exposure: secure record or structured interview	Study controls for age, year, smoking, body mass index (BMI), diabetes mellitus (DM) status	Assessment of outcome: independent blind assessment or record linkage	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts
1	Hod 1991	+	+	+	-	+	-
2	Janssen 1996	+	- (self-report)	+	-	+	-
3	Hod 1996	+	+	+	-	+	-
4	Kimmerle 1997	+	- (self-report)	+	-	-	-
5	Djelmis 1997	+	+	+	-	-	-
6	Ramachandran 1998	+	+	+	-	+	-
7	Moore 2000	+	- (self-report)	+	-	+	-
8	Suhonen 2000	+	- (self-report)	+	-	+	-
9	Sheffield 2002	+	- (self-report)	+	-	+	-
10	Abdelgadir 2003	+	+	++	-	+	-
11	Savona-Ventura 2003	+	- (self-report)	-	-	+	- 58.5%
12	Bo 2004	+	+	+	+	-	-
13	Chico 2005	+	+	+	-	-	-
14	Ricart 2005	+	+	+	-	-	-
15	Sharpe 2005	+	+	+	+	+	-
16	Shefali 2006	+	+	+	+	-	-
17	Abolfazl 2008	+	- (self-report)	+	-	-	-
18	Peticca 2009	+	+	-	+	-	-
19	Fadl 2010	+	+	+	-	-	-
20	Bell 2012	+	- (self-report)	+	+	+	-
21	Vinceti 2014	+	- (self-report)	++	+	+	-

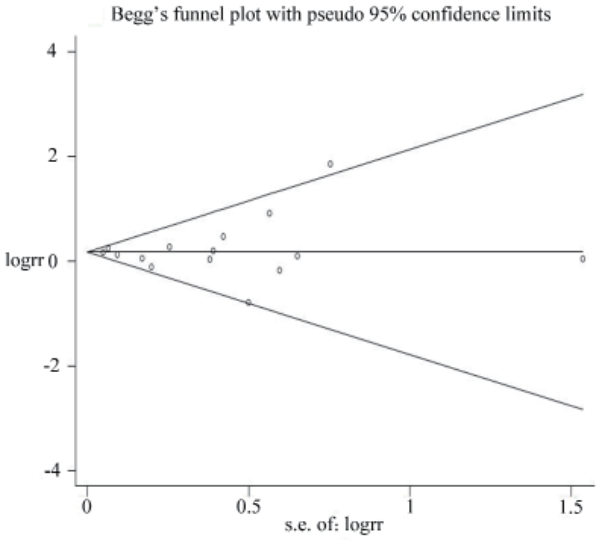

Figure 2. Funnel plot of studies evaluating the association between GDM and congenital malformations. Begg's regression asymmetry test ($p = 0.979$).

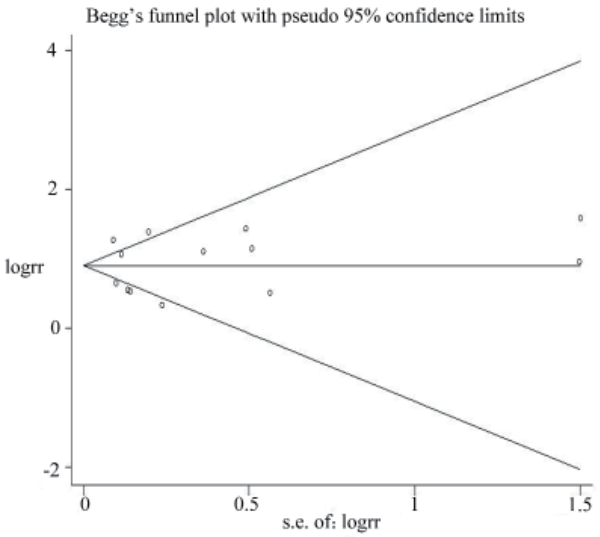

Figure 3. Funnel plot of studies evaluating the association between PGDM and major congenital malformations. Begg's regression asymmetry test ($p = 0.947$).

3.4. *GDM and major congenital malformations*

The pooled RR of GDM from the 17 cohort studies is shown in Figure 4. The meta-analysis of the 17 studies showed a positive association between gestational diabetes mellitus and major congenital malformations (summary RR = 1.18, 95% CI = 1.11-1.26) without noticeable heterogeneity among these studies ($p = 0.342$, $I^2 = 9.9\%$).

3.5. *PGDM and major congenital malformations*

The pooled RR of PGDM from the 13 cohort studies is shown in Figure 5. Compared with GDM, the meta-analysis of the 13 studies showed a stronger positive association between pre-gestational diabetes mellitus and major congenital malformations (summary RR = 2.44, 95% CI = 1.92-3.10) with noticeable heterogeneity

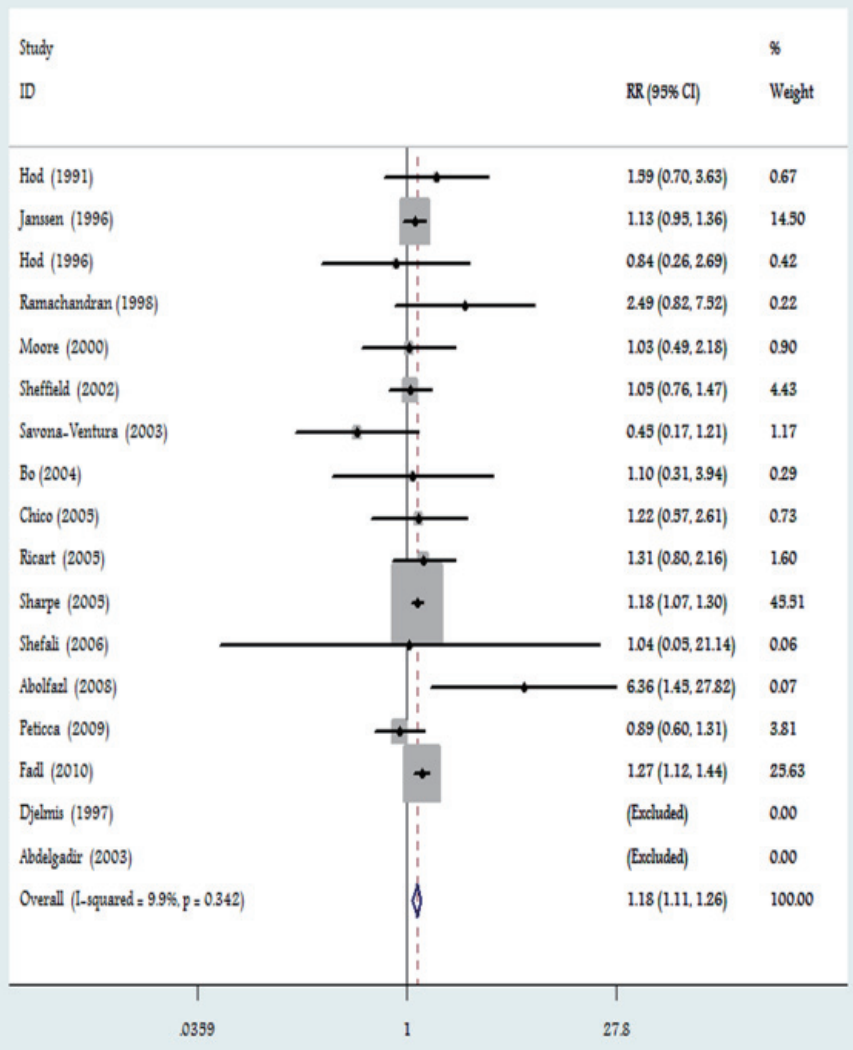

Figure 4. Relative risks (RRs) for the association between GDM and major congenital malformations in 17 studies. The diamond denotes the pooled RR. Shaded rectangles indicate the RR in each study, with sizes inversely proportional to the SE of the RR. Horizontal lines indicate the 95% confidence interval (CI).

among these studies ($p < 0.001$, $I^2 = 78.3\%$). In sensitivity analysis with omission of one study at a time and analysis of the rest, the association between PGDM and major congenital malformations remains unchanged, which suggesting that the heterogeneity may come from factors outside a single study. From the analysis, we found a significant positive association between PGDM and major congenital malformations.

4. Discussion

In this study, we evaluated the effect of maternal diabetes mellitus on congenital malformations of offspring using the results of previous cohort studies. The conclusion of this 25-year meta-analysis is that offspring of GDM women have a mild but distinctly higher risk of major congenital malformations (RR = 1.18, 95% CI = 1.11-1.26) than the reference group. This risk is much lower than that observed in women with established diabetes (RR = 2.44, 95% CI = 1.92-3.10). However, the role of etiologic factors, such as age, obesity or hyperglycemia still cannot be ascertained. Several opinions on potential links between maternal diabetes mellitus and the risk of congenital malformations have been proposed.

The pathogenesis of major congenital malformations of all types is complicated and has possibly a multifactorial origin (*32,33*). The link between hyperglycemia and congenital anomalies has been established, but the precise mechanism it occurs has not been completely elaborated. It is supposed that hyperglycemia could cause damage to the developing yolk sac, an increased production and liberation of free oxygen radicals, deficiency of myoinositol and arachidonic acid and a disruption in signal transduction (*34*); increasing evidences suggest that embriopathies may be connected to a disruption in intracellular signaling by inositol-derived effectors and prostaglandin precursors such as arachidonic acid (35). As a result of the presence of these fuels, some type of genotoxic effect might occur which could cause morphologic damages in the fetus (*33,36*). Nowadays, there is compelling evidence linking epigenetic factors to GDM. Some

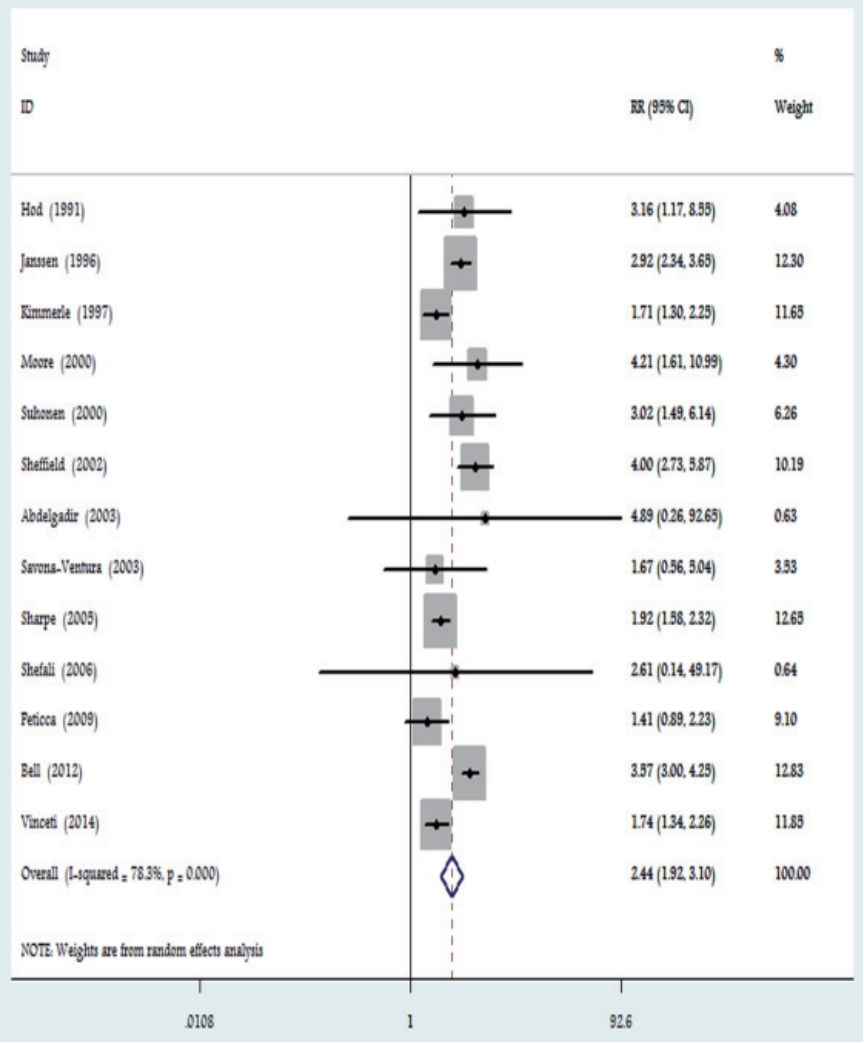

Figure 5. Relative risks (RRs) for the association between PGDM and major congenital malformations in 13 studies. The diamond denotes the pooled RR. Shaded rectangles indicate the RR in each study, with sizes inversely proportional to the SE of the RR. Horizontal lines indicate the 95% confidence interval (CI).

epigenetic alterations mainly related to beta cell function and intrauterine growth retardation have been described recently. These alterations could result in reduction of expression of PDX-1, a transcription factor that regulates beta cell development (*37*). And it is important to note that epigenetic effects are defined as heritable changes to DNA structure that do not involve changes to the DNA sequence. Previous studies have showed that folic acid, that is a methyl donor, which prevents genomic damage in human lymphocytes in vitro and maybe also the cytotoxicity, genotoxicity, and perhaps have cytostatic effects on the human genome. However, randomized trials recently have confirmed that periconceptional supplementation with folic acid can reduce the frequency of midline embryonic defects, as well as heart defects, orofacial clefts and miscarriages (38).

Negrato *et al*. hold that pre-gestational diabetes can predispose the fetus to many alterations in organogenesis and growth restriction (*39*), and all fetal adverse pregnancy outcomes are closely related to poor glycemic control during the organogenesis period. Hyperglycemia during the periconceptional period is probably the major teratogenic existing factor, the increased risk of congenital abnormalities found in diabetic mothers seems to be associated to poor metabolic control during the period of organogenesis that occurs in the first trimester of pregnancy probably due to the negative impact of a hyperglycemic milieu in the growing fetus (*33*). But obesity, hypertension and other factors associated with the metabolic syndrome might also be relevant (40).

Our meta-analysis has several strengths. First, the number of cases included was large, suggesting the solid evidence in evaluating the epidemiologic association between maternal diabetes mellitus and congenital malformations risk. Second, the included studies were conducted in different countries, making the results more acceptable. Third, based on the NOS, all of the studies included in this meta-analysis were of high or intermediate quality, making the results more reliable. However, our meta-analysis also has several limitations. First, we cannot to perform a

meta-regression analysis to evaluate the influence of variables such as age and BMI on the risk of MCM because of these variables were not always available. Second, the diagnostic criteria of GDM in some of the studies were based on self-report, which may lead to some misclassification. However, earlier studies have shown that self-reported responses for many common chronic diseases such as DM are reliable compared with medical record (*41*). In our analysis, we did not find significant different RRs between studies using medical records, or blood level as a means of DM diagnostic criteria and using self-report data to determine GDM status. Another limitation is methodological issue related to study design. Although nearly all the cases were confirmed after delivery, reporting may be not completed. Some misclassification of outcome is likely to occur. Finally, maternal diabetes mellitus and congenital malformations share several risk factors that may confound the relationship. However, confounding cannot be fully excluded because our analyses were based on observational studies.

In summary, our analysis further confirms that maternal diabetes mellitus is associated with an increased risk of congenital malformations. With a worldwide increasing prevalence of GDM, the incidence of congenital malformations may increase. Our findings furthermore underline the importance of preventing the emerging worldwide epidemic of GDM. These results suggest that more aggressive management is needed for pregnant women with PGDM and GDM.

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