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

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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...
studies attributable to heterogeneity, we used the I² statistic (18). A fixed-effect model was used to evaluate the RR and 95% CI if no significant heterogeneity (p > 0.05 and I² < 50%) existed. Otherwise, a random-effect model was selected. For I², 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 |
|-------------------|---------|--------------|-----|------|-----------|
| Hod/1991          | Israel  | ADA          | 26  | 8  | 7         |
| Janssen/1996      | USA     | NP           | 242 | 111| 214       |
| Hod/1996          | Israel  | ADA          | 4   | 9  | 470       |
| Kimmerle/1997     | Croatia | WHO (IGT/GDM)| 0   | 50 | 2,402     |
| Djelmis/1997      | Croatia | NDDG         | 5   | 5  | 8         |
| Ramachandran/1998 | India   | NDDG         | 0   | 4 | 0         |
| Moore/2000        | USA     | NP           | 7   | 4 | 299       |
| Suohonen/2000     | Finland | NP           | 30  | 8 | 735       |
| Sheffield/2002    | USA     | NDDG         | 25  | 2,075| 142,509|
| Abdelgadir/2003   | Sudan   | WHO (DM)     | 3   | 0 | 50        |
| Savona-Ventura/2003| Malta | OGGTT*       | 4   | 3 | 318       |
| Bo/2004           | Italy   | C and C      | 3   | 315| 496       |
| Chico/2005        | Spain   | C and C/NDDG | 7   | 83 | 5,844    |
| Ricart/2005       | Spain   | ADA/NDDG     | 71  | 133| 8,451    |
| Sharpe/2005       | Australia| OGGTT**     | 405 | 96 | 14,257   |
| Shefali/2006      | India   | ADA/WHO      | 2   | 3 | 0         |
| Abolfazl/2008     | Iran    | NP           | 4   | 3 | 350       |
| Peticea/2009      | Canadian| NDDG         | 26  | 18 | 727       |
| Fadl/2010         | Sweden  | OGGTT***     | 242 | 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; OGGTT*, 2 h post-OGTT ≥ 8.6 mmol/L; OGGTT**, 2 h post-OGTT ≥ 8.0 mmol/L; OGGTT***, 2 h post-OGTT ≥ 9.0 mmol/L; NP, Not Provided.

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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.
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
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

![Figure 5. Relative risks (RRs) for the association between PGDM and major congenital malformations in 13 studies.](image)
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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