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MATERNAL-FETAL MEDICINE

Association of maternal iron deficiency anemia with the risk of gestational diabetes mellitus: a meta-analysis

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Abstract

Purpose The aim of the study was to conduct a meta-analysis investigating the association of maternal iron deficiency anemia (IDA) and risk of gestational diabetes mellitus (GDM).

Methods Literature search was conducted in various database websites such as PubMed, Cochrane Library, and Web of Science up to 17 June 2018 for related publications written in English. Selected data were extracted from the included studies and were subjected to statistical analysis. Odds ratios (ORs) and 95% confidence intervals (CIs) were computed, pooled, and interpreted. Subgroup analysis by ethnicity (Asians vs. Caucasians) was also performed.

Results Six studies with a total sample size of 15,157 from various countries were included in this meta-analysis. Pooled ORs of all publications included show that pregnant women with IDA have a reduced risk of developing GDM (OR 0.61; 95% CI 0.47–0.80; $P^A = 0.0003$). Subgroup analysis, on the other hand, showed significant associations among Asians (OR 0.60; 95% CI 0.45–0.79; $P^A = 0.0003$) than Caucasians (OR 0.76; 95% CI 0.32–1.76; $P^A = 0.52$).

Conclusion Results of this meta-analysis suggests that pregnant women with IDA are 39% less likely to develop GDM. However, more studies are needed to confirm the claims of our results.

Keywords Maternal iron deficiency anemia · Pregnancy outcomes · Gestational diabetes mellitus · Meta-analysis

Introduction

Anemia is defined as a condition of decreased oxygen-carrying capacity of red blood cells to the tissues caused by lower than normal hemoglobin (Hb) levels [1]. It affects all age groups but is seen more prevalent among non-pregnant women (29%), pregnant women (38%), and children (43%) [2]. Anemia is said to affect an estimated of 56 million pregnant women worldwide and is considered as a significant threat to public health [3]. The most common form of anemia in pregnancy is caused by iron deficiency [4]. Iron, an essential metal needed in the synthesis of Hb, also functions in the synthesis of enzymes required for the production of cellular energy [5]. Women with poor levels of iron are at risk for developing anemia during pregnancy [4]. Normally, blood volume among pregnant women increases as a result of hemodilution which later on leads to the physiologic decreased in the concentration of Hb. The physiologic changes in the blood are even aggravated by the depletion of maternal iron stores caused by the growing feto-maternal unit and as a result, iron deficiency anemia occurs during pregnancy [6, 7].

Studies have suggested that anemia is commonly considered as a risk factor for poor pregnancy outcomes [8–11] and can result in complications that can threaten both mother and fetus. But interestingly, it has been hypothesized that maternal iron deficiency anemia (IDA) is independently associated with a reduced incidence of gestational diabetes mellitus (GDM) [12, 13]. However, only few studies were conducted that focused on the role of IDA in the development of GDM [12–15]. One study mentioned that higher incidence of GDM (10.9%) is seen among non-anemic pregnant women

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than pregnant women with IDA (4.6%) [13]. Little is still known about the relationship of anemia, specifically IDA, with diabetes or GDM due to the limited number of studies [12–14] conducted.

Majority of studies seen in database websites focused mainly on the association of anemia with various adverse pregnancy outcomes such as preterm birth, low birth weight, fetal impairment, and feto-maternal deaths. Hence, the relationship of IDA and GDM among pregnant women was not clearly emphasized. In order to fully understand the underlying pathophysiological mechanism of maternal IDA and its possible relation with GDM, this meta-analysis was performed. It aimed to obtain more precise estimates by pooling the results of the available publications and to statistically increase the power of the individual studies.

Materials and methods

Search strategy

Literature search and article selection were carried out using a combination of the following key search terms: "maternal anemia", "pregnancy outcomes", and "gestational diabetes mellitus" in English. MEDLINE using PubMed, Cochrane Library, and Google Scholar were thoroughly searched for publications as of 17 June 2018. The titles and abstracts of the selected studies were screened to filter appropriate studies; full texts of the resulting publications were evaluated carefully, and references cited in the retrieved publications were manually screened to identify additional eligible articles.

Study selection

The following inclusion criteria were used: (1) studies with data on the incidence of GDM in a case–control design; (2) studies that grouped their respondents into anemic and non-anemic participants; (3) publications written in English; (4) maternal IDA defined as having a Hb level of < 12 mg/dL; and (5) the use of 75 g oral glucose tolerance test as the determinant of GDM. All studies identified were investigated independently for eligibility by two of the authors.

Data extraction

Two authors independently extracted data and reached an agreement on all the items. For each eligible study, the following information was extracted: the first author's last name, publication year, country and ethnicity of the participants, total number of participants, number of anemics vs. non-anemics, and number of patients with GDM.

Quality assessment of the included studies

The Newcastle–Ottawa Scale (NOS) assessment was used to check for the quality of the eligible studies. Selected studies were judged based on three perspectives: selection, comparability, and exposure. The rating system has scores ranging from 0 to 9 points. Studies scoring 5–6 and ≥ 7 points were regarded as moderate and high-quality studies, respectively [16].

Statistical analysis

Statistical analysis for this study was carried out using Review Manager 5.3 (Copenhagen: Nordic Cochrane Centre, Cochrane Collaboration, 2014). The protocol used for this meta-analysis was based on the procedure of Pabalan et al. [17–19]. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were obtained using either the fixed-(absence of heterogeneity) [20] or random-effects (presence of heterogeneity) [21] model. Heterogeneity among the studies was evaluated using χ^2-based Q test [22] and the degree of inconsistency was measured using I^2 statistics [23]. Due to the low power of the test [24], p value (P^{H}) was set at 0.10 for heterogeneity testing. Subgroup analysis was also performed and was based on ethnicity (Asian vs. Caucasian). All p values (P^{A}) were two-sided with significance threshold set at < 0.05 except for heterogeneity estimation.

Sensitivity analysis and publication bias

Sensitivity analysis was used to test for the robustness of the summary effects. In this analysis, the influence of each study in the pooled ORs was examined by repeating the meta-analysis and omitting one study at a time. Publication bias was no longer estimated due to the low sensitivity of the test when the number of studies is < 10 [25].

Results

Characteristics of the included studies

Summary of literature search is presented in Fig. 1, whereas the feature and characteristics of the included publications are summarized in Table 1. Year of publication of the articles ranged from 1996 to 2010. Overall, a total sample size of 15,157 with a wide range of sample sizes across all studies (234–10,942) were included in the meta-analysis. All the enrolled studies contained case–control data in the context of anemic and non-anemic pregnant women. Of the studies selected, five were carried out in Asia [11–15], and

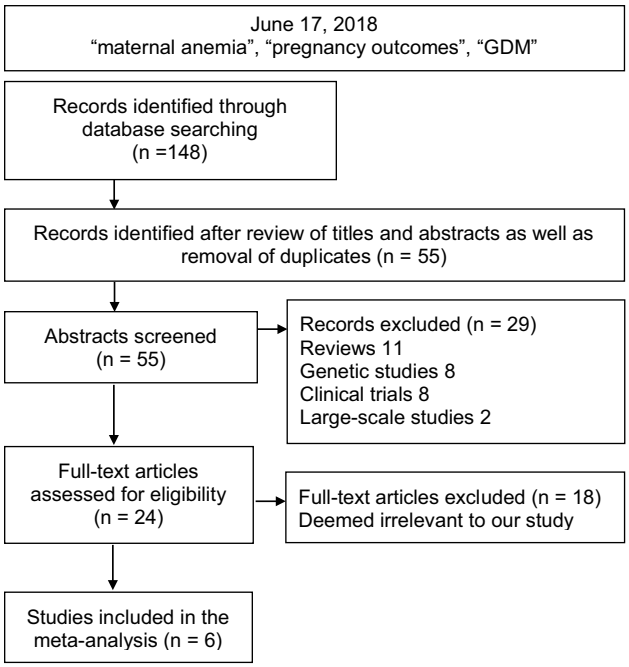

Fig. 1 Summary of literature search. *GDM* gestational diabetes mellitus

the remaining study was conducted in North America [8]. NOS scoring showed the mean and standard deviation to be 6.3 ± 0.2 and a median of 6 indicating that the included studies were of moderate quality.

Meta-analysis result

The six included studies provided the proportion of GDM patients among anemic and non-anemic groups. The fixed-effects model (Fig. 2) showed a significant association between maternal IDA and risk of GDM (OR 0.61; 95% CI 0.47–0.80; $P^{A} = 0.0003$). Homogeneity ($I^2 = 0\%$, $P^{H} = 0.68$) was observed on the pooled analysis indicating the combinability of the individual studies. Based on the pooled ORs, pregnant women with IDA are 39% less likely to develop GDM.

Subgroup analysis was performed by stratifying the studies based on ethnicity (Asians vs. Caucasians), wherein homogeneity ($I^2 = 0\%$) was observed across the two levels of comparison. However, upon stratification, the association of maternal IDA with the risk of GDM was significant among Asians (OR 0.60; 95% CI 0.45–0.79; $P^{A} = 0.0003$), but non-significant among Caucasians (OR 0.76; 95% CI 0.32–1.76; $P^{A} = 0.52$) using the fixed-effects model (Fig. 3).

The influence of the individual study on the overall pooled OR was assessed by systematical deletion of one study at a time. Outcomes of the study were found to be

Table 1 Characteristics of the included studies

First author	R	Year	Country	Ethnicity	*N*	Case/controls	GDM	NOS
Turner	[8]	2010	North America	Caucasian	525	186/339	27	7
Lao	[11]	1996	Hong Kong	Asian	10,942	817/10,125	82	6
Lao	[12]	2002	Hong Kong	Asian	730	175/555	94	7
Lao	[13]	2004	Hong Kong	Asian	726	242/484	60	6
Wani	[14]	2005	India	Asian	2000	1250/750	75	6
Tarim	[15]	2003	Turkey	Asian	234	121/132	20	6

R reference number, *N* total number of participants, *GDM* total number of participants with GDM, *NOS* Newcastle–Ottawa Scale

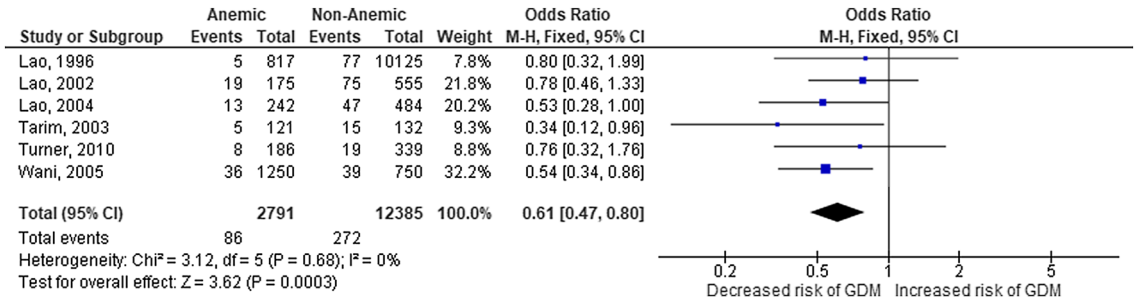

Fig. 2 Forest plot analysis for the overall association of maternal anemia with risk of GDM. *CI* confidence interval, *df* degrees of freedom, *GDM* gestational diabetes mellitus

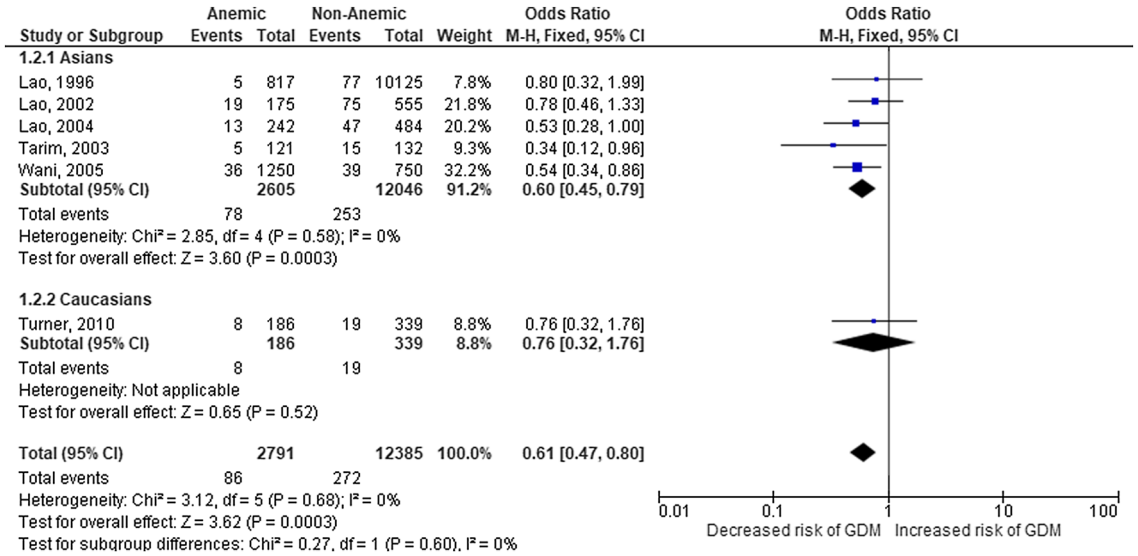

Fig. 3 Forest plot analysis for the subgroup association of maternal anemia with risk of GDM. *CI* confidence interval, *df* degrees of freedom, *GDM* gestational diabetes mellitus

Table 2 Sensitivity analysis of the included studies

	Association		Heterogeneity		Omitted study	Association		Heterogeneity	
	OR (95% CI)	P^A	I^2 (%)	P^H		OR (95% CI)	P^A	I^2 (%)	P^H
Overall analysis	0.61 (0.47–0.80)	0.0003*	0	0.68	Turner et al. [8]	0.60 (0.45–0.79)	0.0003*	0	0.58
					Lao et al. [11]	0.59 (0.45–0.79)	0.0003*	0	0.60
					Lao et al. [12]	0.56 (0.41–0.77)	0.0003*	0	0.72
					Lao et al. [13]	0.63 (0.47–0.85)	0.002*	0	0.58
					Wani et al. [14]	0.64 (0.47–0.89)	0.008*	0	0.60
					Tarim et al. [15]	0.68 (0.48–0.84)	0.002*	0	0.78

OR odds ratio, *CI* confidence interval, P^A *p* value for association, I^2 degree of heterogeneity, P^H *p* value for heterogeneity

*Significant at *p* value < 0.05

robust suggesting the stability of our findings (Table 2). This is evident by the non-significant change in the association and heterogeneity after the analysis.

Discussion

Significant findings of the study provide strong evidence of the potential association of maternal IDA with GDM. This evidence, based on consistent outcomes of significance, is supported by the homogeneity of the results indicating combinability of the study. Furthermore, high magnitude, consistent precision of effects, and robustness enhance the level of evidence presented in this meta-analysis.

Maternal IDA and GDM

The present meta-analysis summarized the results of six studies, involving 15,157 participants. By combining all the ORs and 95% CIs from the individual studies, we showed the association between maternal IDA and risk of GDM. Our results suggest that pregnant women with IDA are less likely to develop GDM (OR 0.61; 95% CI 0.47–0.80; P^A = 0.0003).

Maternal IDA is a serious public health issue and is said to be associated with certain pregnancy outcomes [9, 10]. Hb measurements during the first antenatal visit have become a standard for pregnant women to determine possible risks of feto-maternal complications [12]. Maternal Hb levels not only reflect nutritional status but also the degree of hemodilution, both of which impact

adverse pregnancy outcomes [26]. However, no direct association can be attributed with the effect of Hb levels to GDM. Most studies were conducted among non-pregnant individuals suggesting that high Hb and red cell concentrations among diabetics are due to the elevated glycosylated fraction. Since glycosylated Hb has high affinity for oxygen, increased levels can lead to tissue hypoxia. As a compensatory mechanism, this would trigger the body to produce more red cells and Hb [27–29]. But in the case of pregnant women, lower levels of Hb are associated with GDM. No clear mechanism can yet explain the association of the two; however, studies suggest that the relationship between Hb concentration and incidence of GDM is just a reflection of the relationship between maternal iron stores and GDM [30–32].

During pregnancy, it is estimated that approximately 19.2% of pregnant women develop IDA due to the depleting maternal iron stores with advancing gestation [33–35]. Requirement for iron usually increases during the second and third trimesters of pregnancy caused by the growing feto-placental unit and the expansion of the maternal erythrocyte mass. Iron requirements during pregnancy are high and difficult to achieve by diet alone [36]. According to some studies, concentration of serum iron has a positive linear association with GDM [37, 38] and impaired glucose tolerance [11, 13, 39–41]. Hence, increased levels of iron in serum may play a role in the pathophysiology of GDM.

Association of increased GDM risk with increased iron concentration is biologically plausible. Increasing evidence of the influence of iron with glucose metabolism, even with the absence of iron overload, has been suggested by some studies [42, 43]. Iron is said to catalyze several biochemical reactions that leads to the formation of reactive oxygen species such as hydroxyl radicals [44]. The oxidation property of iron is said to contribute to the increased risk of diabetes in general. Several mechanisms of the role of iron in the pathophysiological development of GDM and other types of diabetes have been proposed. One study suggested that iron overload can lead to β-cell toxicity and dysfunction which in turn leads to impaired glucose metabolism [45]. Another study suggests that increased hepatic and pancreatic accumulation of iron impairs insulin synthesis. Also, in iron overload, tissue deposition of iron decreases cellular glucose uptake [46]. Last, iron is said to interfere with the action of insulin and impairs glucose entry into the adipocytes resulting into overt hyperglycemia [47]. Therefore, it is suggested that the level of body iron stores may play a role in GDM development due to its effect with insulin secretion and function. However, further studies are needed to verify this claim.

Maternal IDA and ethnicity

Subgroup analysis by stratification showed that clinical heterogeneity exists when the studies are sub-grouped by ethnicity. In the present study, significant associations were noted among Asians (OR 0.60; 95% CI 0.45–0.79; $P^A = 0.0003$), in contrast to the insignificant relationship seen among Caucasians (OR 0.76; 95% CI 0.32–1.76; $P^A = 0.52$). There are many factors that can be attributed with these results. First, the diet of Asians differs from those coming from Western countries, which may lead to variations in the prevalence of anemia [48, 49]. Second, this may be attributed also to the genes of the ethnic groups [50, 51]. One study suggested that Asian ethnicity increases the odds of suboptimal iron status by almost five times compared to those with European ethnicity [50]. Finally, the machines and reagents being used for measuring Hb and the oral glucose tolerance were not the same in different places, which might have caused the inconsistencies in the results between Asia and the other locale. Further studies are still required to determine the association of maternal IDA with ethnicity.

Limitations of the study

Overall, findings of this meta-analysis suggest that low serum iron levels associated with maternal IDA is protective against GDM. However, interpreting this study warrants awareness of its limitations, namely (1) the wide range of patient samples sizes in the studies emphasized the results from larger studies while masking those coming from small studies; (2) limited number of studies included in the Caucasian strata which resulted in the decreased power of the resulting pooled effects; and (3) risk of GDM may be attributed to other factors such as environmental, genetic, and maternal characteristics which were not examined in this meta-analysis.

Conclusion

To our knowledge, this is the first meta-analysis that directly investigated the association of maternal IDA with GDM. With this approach, we hope we have contributed to (1) better understanding of the pathophysiological mechanism of GDM, (2) establishing ways of early detection and effective prevention of GDM, and (3) impact current clinical practice guidelines in the management of maternal IDA. Generally, our results suggest that pregnant women with IDA are less likely to develop GDM based on the calculated pooled ORs. However, given the limitations mentioned above,

these findings should be treated with caution when applied to clinical practice.

We recommend for future investigations that would warrant a large-scale prospective cohort study to be conducted due to the limitations of this meta-analysis and as well as the individual studies tested. Other possible risk parameters such as environmental conditions, climate change, behavioral changes, ethnicity, and gene anomalies are recommended to be tested as well. Also, maternal characteristics such as body mass index, maternal age, age of gestation, and iron supplementation should be taken into consideration. We also recommend for future investigators to elaborate more the role of iron in the pathophysiology of GDM.

Author contributions RET: Project development, data collection, data analysis, manuscript writing. EA: Data collection, data analysis, manuscript writing. BC: Data analysis, manuscript writing. MRP-C: Project development, data analysis, manuscript writing.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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