Association between Folic Acid and Gestational Diabetes Mellitus: A Systematic Review and Meta-Analysis Coils

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ABSTRACT

Coronary despite beneficial outcomes in preventing neurogenic defects in fetus, folic-acid significant correlation with gestational diabetes mellitus have recently been demonstrated by a number of published studies. Therefore, our aim was to compare women taking low versus high folic-acid supplements before/during pregnancy period in association to the development of Gestational Diabetes Mellitus (GDM) in the second/third trimester, by systematic review of literature and meta-analysis. PubMed, EMBASE and Clinical Trials.gov were systematically searched for observational studies assessing clinical outcome in terms of GDM diagnosis, between women taking high folic-acid supplements doses versus low folic-acid supplements doses before/during pregnancy. High folic-acid supplement dose was defined as >400 ug/day of folic acid supplements for >90 days prior/during conception, while low folic-acid supplement dose was defined as consuming <400 ug/day of folic-acid supplements for <30 days prior/during pregnancy. Main outcome was development of GDM during second/third trimester. The outcome/dependent variable was treated as a dichotomous-nominal variable (i.e. developed/not-developed GDM). Risk ratio was the outcome measures for each comparison group, while Odds Ratio was used as overall-effect measure for two comparison groups. Overall effect was diagrammatically illustrated by forest-plots and funnel-plots utilizing computer software, Review Manager Version 5.3. Fixed-effect model was used when I^2 was <50% and random-effect model was used if I^2 was >50%. Thirteen (13) studies reported a total of 42,780 participants, of which, 27,278 had taken adequate folate while 15,502 had taken inadequate folate. Eight (62%), three (23%) and two (15%) included studies showed increased risk, reduced risk and no association, respectively, between comparison groups. The risk of developing GDM was 70% higher in women taking higher/adequate folic acid supplements than those taking lower/inadequate folate doses; OR=1.70, p-value=0.03, at 95%; C.I:1.04-2.78. Therefore, high/adequate folate intake before or during pregnancy positively correlates with increased risk of GDM in the second and third trimester.

Keywords: Gestational diabetes mellitus; Pregnancy diabetes mellitus; Folic acid; Folate; Vitamin B9; Neuro-tube defects; Insulin resistance; Systematic review; Meta-analysis

KEYWORDS

- gestational diabetes mellitus
- pregnancy diabetes mellitus
- folic acid
- folate
- vitamin B9
- neuro-tube defects
- insulin resistance
- systematic review
- meta-analysis

Introduction

With an estimated overall adult prevalence of about 6 to 13 in the United States, diabetes mellitus utilizes more personal health care resources than any other disease condition [1, 2]. Defined as fasting blood glucose level of more than 7 mmol/L, glycated Hemoglobin of more than 6.4% or 2-hour post-load glucose on the 75

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g OGTT (Oral Glucose Tolerance Test) of more than 11 mmol/L, type 2 diabetes is more prevalent than type one [3,4]. Apart from type-one which is mostly caused by autoimmune destruction of beta-pancreatic cells, type two Diabetes Mellitus is by far adult onset precipitated by sedentary lifestyles leading to increased insulin resistance [5]. Insulin resistance constitutes to the most prevalent endocrine derangements in the world. Defined by subnormal response of a given level of insulin, Insulin resistance is closely associated with other major diseases of global reach than just diabetes [6,7]. The spectrum of these associated diseases ranges from atherosclerosis, nonalcoholic fatty liver disease, ovulatory dysfunction, obesity, Rheumatoid arthritis and pregnancy [6,8,9]. The physiology of normal pregnancy involves maternal physical and metabolic adjustments to accommodate the fetus. Among metabolic adjustments is increased secretion of growth hormone, corticotrophin-releasing hormone, placental lactogen (chorionic somatomammotropin), prolactin, and progesterone [10]. Primarily, these hormones are aimed at ensuring adequate supply of vital nutrients to the developing fetus, but unfortunately could also leads to increased maternal insulin resistance in pancreatic incompetent women, ultimately leading to gestational diabetes mellitus [11]. On the other hand, developing fetus requires loads of nutritional supplies in their correct proportions [12]. Among many, is folate (Vitamin B9) which is shown to reduce the risk or prevent development of neuro-tube defects in early stages of a developing embryo [13]. Despite being widely available in daily regular foods like beef, liver, leafy vegetables, peas and beans, avocados, eggs, and milk, the supply of folate to a developing fetus was deemed inadequate, necessitating worldwide practice of additional folate supplements in all pregnant women or those planning to become pregnant [13-15]. This practice, by far, reduced the incidents of neuro-tube defects but concerns arose after recent reports of significant associations of folic acid with development of gestational diabetes mellitus in second and third trimesters [16-19]. To assess further on the claimed significant correlations between folic acid and gestational diabetes mellitus, our study seeks to compare low versus high maternal folic acid intake in pre/during pregnancy period and development of gestational diabetes, by systematic review of literature and meta-analysis.

Literature Review

▪ Eligibility criteria

This study included two kinds of participants; women taking high/adequate folic acid supplements doses versus women taking low/inadequate folic acid supplements doses before/during pregnancy. High/adequate folic acid supplement dose was defined as consuming more than 400 ug/day of folic acid supplements for more than 90 days prior or during conception, while low/inadequate folic acid supplement dose was defined as consuming less than 400 ug/day of folic acid supplements for less than 30 days prior or during conception [20]. Studies using same participants as their own controls in subsequent pregnancies, as well as studies using matched/unmatched participants will be eligible for inclusion. In this study, no demographic restrictions be taken into account in that, all pregnant women fulfilling folate criteria were deemed eligible. Only observational studies, excluding reviews, assessing suitable outcome (i.e. Gestational Diabetes Mellitus diagnosis) between the two participants groups (i.e. women taking low versus high folic acid supplements before/during conception) were eligible for inclusion. To extend study search, published and unpublished literatures were sought for inclusion. To increase the external validity of this study, accessible literature from all around the world were eligible for inclusion as long as they fulfill other aforementioned inclusion criteria. Only English published literatures were eligible for inclusion.

▪ Information sources

Three online databases, namely PubMed, EMBASE and the ClinicalTrials.gov were searched to come up with eligible studies for inclusion. The searches were not customized for searching within any restricted date ranges. First and/or corresponding authors of articles searched were contacted to provide further information or settle unclear information. Secondary referencing of eligible studies was done to extend the search scope. To access online databases, Central South University Library website was used: http://lib.csu.edu.cn/

▪ The search

To generate a set of citations that are relevant to our study's search question, advanced search tool was used in all of the three databases aforementioned.

Of three databases, PUBMED is presented here. Using PubMed, advanced search builder was customized to 'all fields', 'human species' and different combination of key words were run for search; ("folic acid"[MeSH Terms] OR ("folic"[All Fields] AND "acid"[All Fields]) OR "folic acid"[All Fields] OR "folate"[All Fields]) AND ("diabetes, gestational"[MeSH Terms] OR ("diabetes"[All Fields] AND "gestational"[All Fields]) OR "gestational diabetes"[All Fields] OR ("gestational"[All Fields] AND "diabetes"[All Fields])). The search was also done using: vitamin B9 [Title/Abstract] AND Gestational diabetes [Title/Abstract]. These searches were independently performed by two authors; Pijush Sarker and Andrew Joabe. Search results were exported to computer software, EndNoteX9, which was used to manage and keep track of references throughout this study.

Study selection process

All studies resulting from online database search independently conducted by two authors were screened by their titles and abstracts to initially assess their relevance to our study question. This was, level-one screening, and was done by same two authors; Pijush and Andrew. Compiled results of level-one screening were then be searched for their full-text articles. Level-two screening involved assessing the retrieved full text articles for eligibility for inclusion or exclusion, basing on our preset study inclusion criteria. Any differences of thoughts in the search and selection process were settled by the third author, Zhang.

Data extraction

Before data extraction process from full-text articles meting eligibility criteria for inclusion, assessment for methodological biases was done. STROBE (Strengthening the Reporting of Observational studies in Epidemiology) tool [21] customized for case-control and cohort studies, was used to assess reporting biases for included observational studies. PRISMA (preferred reporting items for systematic reviews and meta-analyses) tool [22] was used for this study write-up to minimize reporting bias. The process of data extraction was independently performed by two authors, namely; Pijush and Andrew. All differences of thoughts in the data extraction process were settled by the fourth author, Shishir Data collected included participants' demographics, study characteristics and reported gestational diabetes diagnoses status in line with our study question. Demographic data and the number of participants in each comparison group were recorded for each of eligible study. Duration and dosage of folic acid supplements taken were recorded, as well as the time during which a woman started taking folic acid supplements (i.e. before or after conception). Any missing or unclear information was retrieved by contacting first or corresponding authors of respective study. In line with this study question, one outcome was recorded from the eligible studies; Gestational Diabetes mellitus diagnosis in the second or third trimester. This outcome was recorded from both comparison groups (i.e. women taking high versus low folic acid supplements before or during pregnancy).

Analysis

Data were analyzed separately according to our outcome of interest. We therefore compared women taking low versus/inadequate/none versus high/adequate folic acid supplements before or during pregnancy period in association to the development of gestational diabetes in the second or third trimester. Risk Ratio (RR) was the outcome measures for each comparison group in cohort study. Odds Ratio (OR) was used as overall effect measure for two comparison groups of women in case-control study. Overall effect was diagrammatically be illustrated by forest-plots and funnel plots utilizing a computer software, Review Manager (RevMan Version 5.3). The software was customized to random or fixed effect model depending on the heterogeneity (I^2) of the studies when analyzing the outcomes. Fixed effect model was used when I^2 was less than 50% and random effect model will be used if I^2 was more than 50%.

Assumptions and Simplifications

For this study purpose, only prescribed folic acid supplements (other than folic acid from dailydiet) was considered in the analysis. Participants presenting with different gestations during the follow-up period were counted multiple times depending on number of gestations. Participants will be considered to have been correctly diagnosed as having gestational diabetes mellitus or not. All participants, despite study country, will be considered to have received standard obstetric care aligning with internationally accepted guidelines.

Results

Study selection

Preliminary literature search identified a total of two hundred and eighty-nine (289) studies that seemed relevant basing advanced online-database searches for published and unpublished articles. Fifty-two (52) articles were duplicates therefore excluded. Two hundred and thirty-seven (237) articles went through level-one screening of titles and abstracts and a hundred and ninety (190) deemed not relevant to our study question. The remaining forty-seven (47) studies were searched for their full text articles and underwent a level-two screening for eligibility criteria for inclusion. Thirty-three (33) studies were excluded for not fulfilling inclusion criteria. Thirteen (13) studies were found to fully fulfill preset eligibility criteria and were up for quality assessment. Figure 1, summarizes search results, screening and selection process. Total number of participants was 42,780, of these, 27,278 had taken adequate folate while 15,502 had taken inadequate folate.

Study characteristics

Table 1 illustrates the study characteristics of all 13 eligible articles included in this study. Of 13 published studies that were captured by the search, 11 were published in full and their full-text manuscripts were found, while in 2 articles were unpublished but otherwise accepted articles [23,24]. Contacts were made with authors of all studies included studies except two, [17,25] in which all required information was readily available. Four (4) studies involved case-controlled, two cross-sectional and other were cohort studies. Studies were performed in different settings from a diverse number of countries all around the world. Seven (7) studies were from Asia, four (4) from Europe Asian countries, one (1) from Americas and Australia each. This was thought to be important to increase the external validity of this study. Eight studies had independently concluded an increased risk of gestational diabetes mellitus with increasing intake of folic acid prior to conception or during pregnancy [17-19,23,24,26-28]. On the other hand, three studies [25,29,30] had independently concluded an reduced risk of gestational diabetes mellitus with increasing

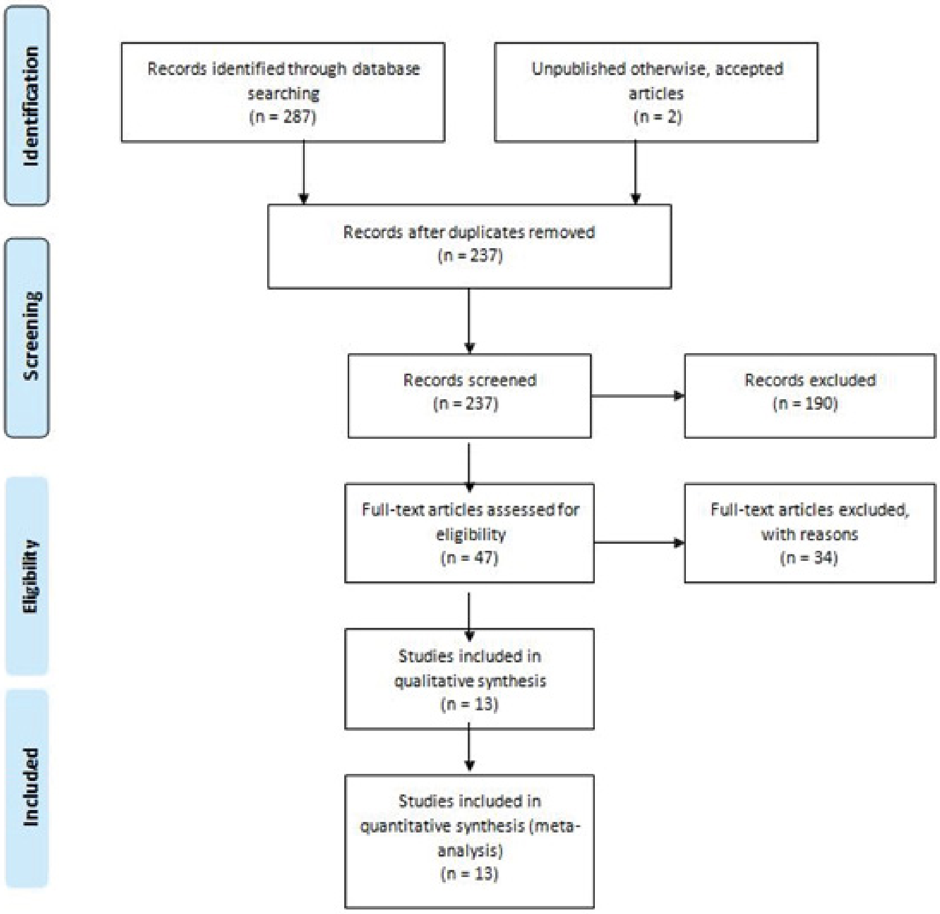

Figure 1: PRISMA 2009 Flow Diagram for study selection.

intake of folic acid prior to conception or during pregnancy while two studies showed there was no association between the variables (Table 1) [31,32].

- **Sources of bias**

Table 2 illustrates the quality assessment of included studies for risk of bias. All 13 eligible studies included in this study were assessed for risk of bias using STROBE tool for case-control, cohort studies and cross-sectional studies. Study size, mean gestation age for included participants, study design, study setting, Duration and dosage of folic acid supplements taken were recorded, as well as the time during which a woman started taking folic acid supplements (i.e. before or after conception) were recorded from all studies. Different studies involved different number sample sizes. Other studies included significantly large number of participants (i.e. 20,199) [25] while other showed as low as 135 [31]. Large sample sizes are more representative of general population as compared to small sample size studies. None of these 13 studies reported to have calculated the required sample size prior to their conduction (Table 2).

A mixture of cohort [18,26,32], cross-sectional [23,24] and case controlled studies [28,29] were found to be eligible for this study as long as they reported risk comparison of gestational diabetes mellitus between adequate versus inadequate folic acid taking women. None of the studies were experimental. Hierarchically, observational studies are considered to have higher risks for biases than experimental studies. This study included both prospectively [19] and retrospectively [28] following up of participants. Prospective studies have lesser information and recall bias risks for bias than retrospective studies. On the other hand, retrospective studies have lesser attrition bias risks (Table 2).This study included articles from various countries all around the world. Of thirteen studies, five took place in China [17-19,24,30], two in United Kingdom [28,31] and one each from Australia [29], Finland [27], India [26], Netherland [32], United States [32] and Singapore [23]. This is valuable in increasing external validity of the study but on the other hand, different settings could also mean different environments for participants in the compiled studies. Lower socioeconomic statuses could also mean limited equipped hospitals hence lower standard of care given to patients as compared to higher socioeconomic countries. None of the studies was from Africa. This could also mean less representation of the global population. This study employed the use of various cut-points to define adequate versus inadequate folate intake. Other studies used duration [17] of folate intake while others used the dosage of folic acid [25] taken. In a contemporary setting, the employment of different cut-points definitions might could introduce selection biases in our study (Table 2). The time that participants in these studies

Table 1: Study characteristics and sources of bias.

Study, Year	Study design	Mean age	Study size (case, Control)	Country of study	GDM Risk with adequate/high Folate
Li S, 2019	Cross-sectional	29.4 ± 4.5	406 (301,131)	China	Increased
Li Q, 2019	Cohort	NR	4353 (25981755)	China	Increased
Li M, 2009	Prospective Cohort	31.8 ± 3.2	20,199 (11741,8458)	United States of America	Decreased
Huang, 2009	Prospective Cohort	28.4 ± 3.15	326 (294,32)	China	Increased
Chen, 2019	Case-Control	NR	9556(7032,2524)	China	Decreased
Martino, 2018	Prospective Case-control	30.4 ± 4.5	135 (76,59)	United Kingdom	No association
Lai, 2017	Cross- sectional	NR	913 (884,29)	Singapore	Increased
Zhu, 2016	Prospective cohort	NR	1938 (1096,842)	China	Increased
Sukumar, 2016	Retrospective Case-control	30.3 ± 5.88	344 (237,107)	United Kingdom	Increased
Meinila, 2015	Prospective cohort	32 ± 5	234 (153,81)	Finland	Increased
Beckman, 2014	Prospective case-control	32.1 ± 4.8	224 (56,168)	Australia	Decreased
Krishnaveni,2009	Prospective Cohort	NR	519 (328,191)	India	Increased
Looman, 2019	Prospective cohort	27.5 ± 1.5	3607 (24821125)	Netherlands	No association

NR-Not Reported

started to use folic acid supplements differ. Other studies recorded folic acid usage prior to conception [29,31] while others recorded while pregnant already during the early pregnancy [19,23,26]. Furthermore, other studies included folic acid intake combined with other macro and micronutrients such as Vitamin B12 [26,28,32]while others only strictly considered only folate [18,19]. This could have contributed to selection as well as information biases (Table 2). All included studies used internationally accepted approaches in diagnosing Gestational Diabetes. This was advantageous to our study as it minimized detection biases.

Risk of Gestational Diabetes

Odds Ratio (OR) was used to compare the risk of developing gestational diabetes mellitus between women taking low versus high folic acid supplements before or during pregnancy period. Using a computer software Review Manager Version 5.3 (RevMan v.5.3), the OR was 1.70, 95% Confidence interval was 1.04, 2.78 with P-value =0.03 (Figure 2). This finding reached statistical significance. Hence, based on this study, there is a significant difference in the risk of developing gestational diabetes between the two comparison groups, in that, women taking higher folic acid supplements are 70% more susceptible to develop Gestational diabetes than those taking inadequate or none. Random effect model was used.

▪ Publication bias

Figure 3 illustrates a funnel-plot for 13 studies that evaluates the risk of developing gestational diabetes lupus flares between women taking low versus high folic acid supplements before or during pregnancy period. This funnel plot was generated utilizing fixed effect model to illustrate publication biases. Pregnant SLE women and non-pregnant SLE women. Smaller sample sized studies at the bottom and medium sample sized studies at the middle of the funnel-plot were more symmetrically distributed as compared to large sample sized studies at the top. This suggest heterogeneity of the study estimates as well as likely publication bias favoring studies with medium to smaller sample sizes than large sample sized. Sensitivity analysis was performed

Table 2: Individual-study bias assessment by STROBE tool.

Study, Year	Selection bias	Information bias	Attrition bias	Detection bias
Li S, 2019	High	High	Low	Low
Li Q, 2019	Low	Low	High	Low
Li M, 2009	Low	Low	High	Low
Huang, 2009	High	Low	High	Low
Chen, 2019	High	Low	High	Low
Martino, 2018	Low	Low	High	Low
Lai, 2017	Low	High	Low	Low
Zhu, 2016	High	High	Low	Low
Sukumar, 2016	Low	High	Low	Low
Meinila, 2015	Low	Low	High	Low
Beckman, 2014	Low	Low	High	Low
Krishnaveni,2009	Low	Low	High	Low
Looman, 2019	Low	Low	High	Low

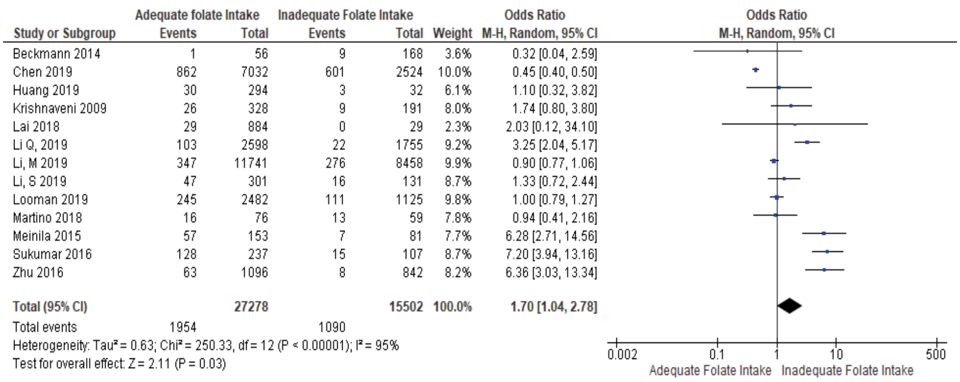

Figure 2: Gestational Diabetes Risk comparison between adequate versus inadequate folate intake.

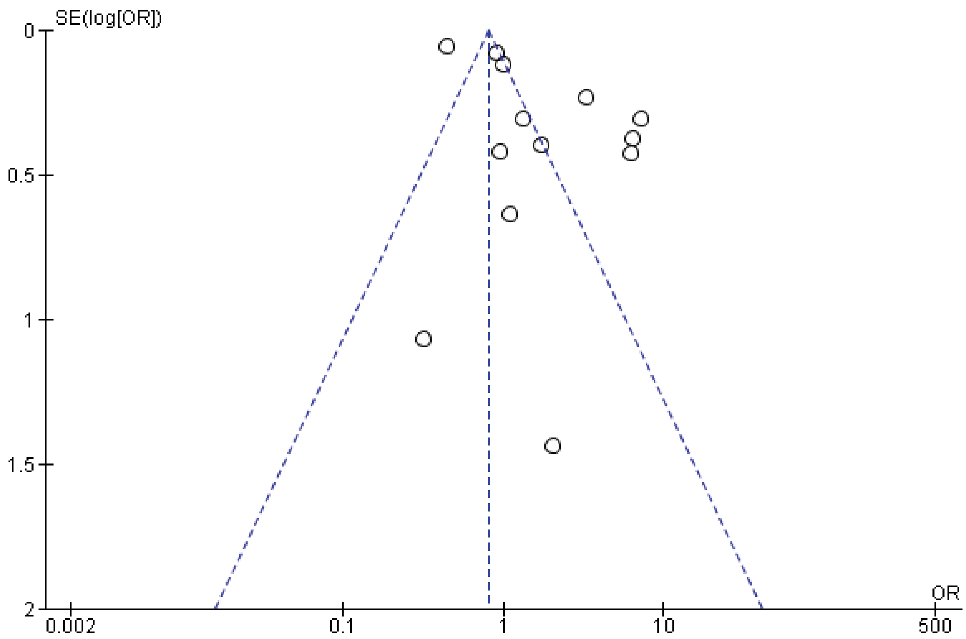

Figure 3: Funnel-plot for 13 eligible studies.

by removing two studies with largest sample sizes, (25,30) but the relationship between increasing folic acid intake and risk of GDM did not change; OR was 1.86, 95% Confidence interval was 1.58, 2.18 with P-value =0.00001.

Discussion

Additional folate supplements in pregnant women or those planning to become pregnant has, by far, reduced the incidents of neuro-tube defects [33,34] but concerns arise after reports of significant associations of folic acid with development of gestational diabetes mellitus in second and third trimesters. A number of studies have previously been published showing contradicting results concerning the effect of folic acid supplementation to the risk of developing gestational diabetes. Other studies have suggested that higher/adequate folic acid supplementation increases the risk, others showing reduced risk while others showing no association at all. This study systematically reviewed and meta-analyzed a total of thirteen (13) studies reporting risk of developing gestational diabetes mellitus between women taking adequate/high versus inadequate/low folic acid supplements before or during pregnancy period and it concluded that high folic acid supplements before or during pregnancy period is associated with increased risk of developing gestational diabetes later in pregnancy than taking lower/none folic acid supplementation (OR 1.70, 95% confidence interval 1.04, 2.78 with P-value=0.03). Women taking high folic acid supplements face 70% increase risk of developing gestational diabetes than those taking lower doses or for shorter durations. The reason and predictors for higher risk of gestational diabetes in women consuming high folate than lower levels of folate supplements could be explained by the association between folic acid uptake and the action of Tumor Necrotic Factor-alpha, an inflammatory cytokine. Aurojo [16] conducted a study to demonstrate the association between folic acid uptake and gestational diabetes and found that GDM modulates folic acid uptake by the syncytiotrophoblast but more importantly, serum leptin levels and TNF-alpha were increased in high serum folic acid contents. On the other hand, other studies showed that high levels of TNF-alpha, IL-6, IL-1, and leptin [35-37]; and lower levels of adiponectin [38], were sole mechanisms for pathogenesis of insulin resistance in rheumatoid arthritis and metabolic syndrome. It follows that, higher levels of TNF-alpha and high leptin, in high folate intake women predisposes them to increased insulin resistance and metabolic syndrome, leading to development of type-2 like diabetes mellitus [39-43]. This is also explained by the fact that high BMI pregnant women are more susceptible to develop gestational diabetes than lower BMI pregnant women [31,33,44-51]. The conclusion for this study aligns with several other studies, though other study designs were used instead of meta-analysis. The quality of meta-analysis study depends also on the quality of the included studies. This posed a loop-hole for biases in this study. Biases observed in included studies in this review were mean age differences between participants, different types of study designs used in different studies, different times of using folate supplements (i.e. prior conception or during early pregnancy), different durations on folate supplements, different cut-off points used to define adequate versus inadequate folate supplements and different socioeconomically diverse study settings (Table 1). More room for bias was, for instance, of all included studies, no study calculated the number of sample size required prior to conducting a study. For observational studies, this poses a risk for increased "type-one statistical error" [32]. Also, none of the included studies explained whether two or more pregnancies from the same participant in different times during the follow-up, were counted as one or multiple participants. This could give an exaggeration of effects. Despite the biases, on the other hand, majority (62%) of studies included in this systematic review and meta-analysis are consistently favoring the fact that taking adequate/high folic acid supplementations are more associated with gestational diabetes mellitus than taking lower/inadequate levels of folic acid prior to conception or during pregnancy.

Conclusion

This systematic review and meta-analysis conclude that high folic acid supplements before or during pregnancy period is associated with increased risk of developing gestational diabetes later in pregnancy than taking lower/none folic acid supplementation. This study urges healthcare providers to lower but not stop folic acid supplements in pregnant or women planning to conceive. The conclusions of this study should be interpreted with care as there were a number of biases identified during the study; therefore, authors of this study call upon more extensive study mitigating biases and probably use experimental study designs than observational studies.

Data Availability

The data supporting this systematic review and meta-analysis study are from previously reported studies and datasets, which have been cited. The processed data are available upon request to individual-study's corresponding author.

Conflicts of Interest

All authors declare no conflict of interest.

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