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NUTRITION

The association between serum selenium and gestational diabetes mellitus: A systematic review and meta-analysis

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ABSTRACT

Background: Results of the studies about association between serum selenium concentration and gestational hyperglycemia are inconsistent. Some studies have demonstrated that women with gestational diabetes mellitus (GDM) have lower Se concentrations while contrary results are reported in other studies.
Aim: The aim of this study is to compare the serum Se concentration in women with GDM and normoglycemic pregnant women via a systematic review and meta-analysis.
Methods: A computerized literature search on four databases (PubMed, Cochrane register of control trials, Scopus and Google scholar) was performed from inception through August 2013. Necessary data were extracted and random effects model was used to conduct the meta-analysis.
Results: Six observational studies (containing 147 women with GDM and 360 normoglycemic pregnant women) were found, which had compared serum Se concentration in women suffering from GDM with normal pregnant ones. Our meta-analysis revealed that serum Se concentration was lower in women with GDM compared to normoglycemic pregnant women (Hedges = −1.34; 95% CI: −2.33 to −0.36; $P < 0.01$). Stratified meta-analysis demonstrated that concentration of Se in the sera of women with GDM was lower than normal pregnant women both in second and third trimesters, but the result was not significant in second trimester (second trimester: Hedges = −0.68; 95% CI: −1.60–0.25; $P = 0.15$, third trimester: Hedges = −2.81; 95% CI: −5.21 to −0.42; $P < 0.05$). It was also demonstrated that serum Se status was lower in pregnant women with impaired glucose tolerance (IGT) compared to normoglycemic pregnant women (Hedges = −0.85; 95% CI: −1.18 to −0.52).
Conclusion: The available evidences suggest that serum Se concentration is significantly lower in pregnant women with gestational hyperglycemia compared to normal pregnant women.
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Introduction

Gestational diabetes mellitus (GDM) as a temporary form of type 2 diabetes mellitus (T2DM) is one of the most prevalent complications in pregnancy [1]. GDM has become more common due to incremental prevalence of obesity and T2DM. Its prevalence varies from 1.7% to 11.7% around the world [2]. During normal pregnancy, insulin resistance increases in parallel with increasing in oxidative stress which leads to reduction in antioxidant levels [3]. These conditions are more prominent in women with GDM; in whom glucose oxidation, protein glycation, and lipid peroxidation lead to free radicals accumulation [1]. It seems that a positive correlation exists between erythrocyte glutathione peroxidase-1 (GPX1) activity and insulin resistance. This can be explained through the fact that oxidative stress reduces insulin secretion and increases insulin resistance; therefore, it is linked toT2DM [3].

Selenium (Se) as an essential trace element has an important role in the action of antioxidants such as glutathione peroxidases (GPxs) [4]. Also, it is proposed that Se has anti-diabetic functions due to its insulin-like characteristics; hence Se supplementation seems to have beneficial effects in diabetic patients [5,6]. It seems that the relationship between low Se concentration and impaired glucose tolerance is exclusive to pregnancy, because some evidences show that serum Se concentration is higher in patients with

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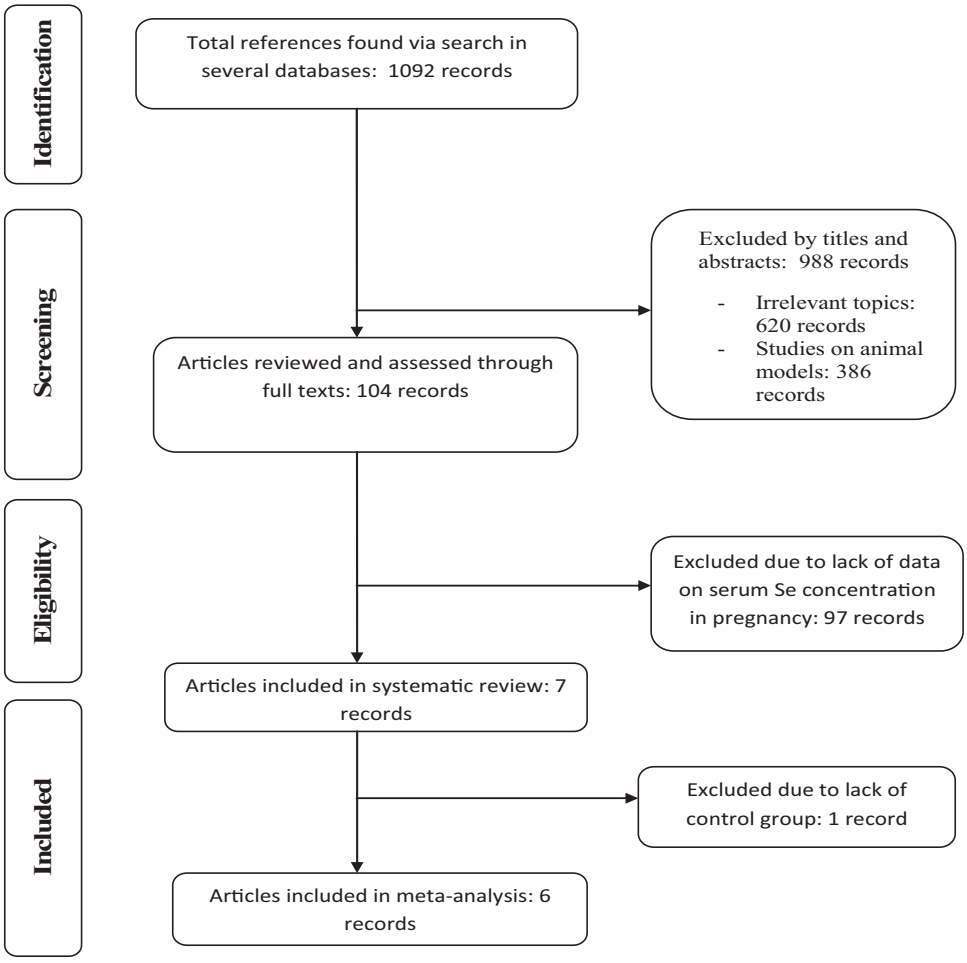

Fig. 1. PRISMA flow diagram of study identification, inclusion and exclusion.

T2DM [7,8]. Stranges et al. also suggested that Se supplementation may increase the risk of T2DM [9]. In a recently published meta-analysis evaluating the effects of Se supplementation on risk of T2DM and cardiovascular disease, the authors concluded that Se supplementation cannot significantly increase the risk of T2DM [10].

The results of the studies about association between selenium status and GDM or gestational hyperglycemia are inconsistent. Some studies have shown that women with GDM have lower concentrations of serum Se compared to healthy pregnant women [11–14]; however, a study performed by Molnar et al. [15] showed that serum Se concentration is significantly higher in GDM patients; while Al-Saleh et al. [16] did not find a significant association between serum Se concentration and GDM.

Referring to the scientific literature, no review article has been published on the association between selenium status and GDM. In the present study, we conducted a meta-analysis on the subject to quantify the association between maternal selenium status and GDM.

Materials and methods

The study protocol was registered in PROSPERO, an international database of prospectively registered systematic reviews in health and social care, with the registration number: CRD42013005038. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria to conduct and report the results of the present study.

Search strategy

A computerized literature search on four databases, i.e., PubMed (http://www.ncbi.nlm.nih.gov/pubmed), Cochrane register of control trials (http://onlinelibrary.wiley.com/cochranelibrary/search), Scopus (http://www.scopus.com/home.url) and Google scholar (http://scholar.google.com) was performed from inception through August 2013. We used keywords selected from Medical Subject Headings (MeSH; http://www.ncbi.nlm.nih.gov/mesh) or other keywords including "Selenium"[Mesh], "Selenium Compounds", "Selenium-Binding Proteins", "selenium*" and "selenate" in combination with "Diabetes, Gestational", "gestational diabetes mellitus", "pregnancy", and "gestation". Two authors evaluated the studies separately through the review of the titles, abstracts, and if necessary, full texts (TJ and AAF). References of related papers were more extensively read by authors to avoid missing articles. Any disagreements in selecting related papers were resolved by debate with a third author (ASA).

Inclusion criteria

Observational studies performed in adult women to assess serum Se levels at any time of gestational period in both pregnant women with gestational hyperglycemia or GDM and healthy pregnant women as their control group were enrolled in the current systematic review and meta-analysis.

Table 1
Characteristics of studies enrolled in meta-analysis.

Study/Year (Design)	Ref. No[a]	GDM[b] (*n*)	IGT[c] (*n*)	NPW[d] (*n*)	Gestational age (week)		Serum Se concentration (μg/L)		
					GDM	NPW	GDM	IGT	NPW
Tan et al., 2001	11	57	98	40	20–33	20–33	66.0 ± 12.0	63.1 ± 13.2	78.5 ± 17.7
(Case control)		83	–	50	33–42	33–42	61.5 ± 13.1	–	70.7 ± 15.2
Al-Saleh et al. 2004 (Case control)	12	15	–	15	39 ± 0.3	40 ± 0.4	75.2 ± 3.1	–	102.3 ± 3.1
Bo et al. 2005 (Case control)	13	29	42	123	24–30	24–30	8.8 ± 1.3*	9.7 ± 1.4*	10.8 ± 1.8*
Al-Saleh et al. 2007 (Case control)	16	10	–	11	38 ± 0.4	40 ± 0.5	85.1 ± 5.4	–	89 ± 4.9
Kilinc et al. 2008 (Cross sectional)	14	30	49	101	24–28	24–28	34.7 ± 8.7	39.9 ± 6.5	50.7 ± 9.8
Molnar et al. 2008 (Case control)	15	17	–	20	24–28	24–28	51.7 ± 11.6	–	40.5 ± 8.0

* μmol/L.
[a] Reference number.
[b] Gestational diabetes mellitus.
[c] Impaired glucose tolerance.
[d] Normal pregnant women.

Exclusion criteria

Studies compared normal pregnant women with diabetic or hyperglycemic pregnant women (meaning that they were diabetic or hyperglycemic before pregnancy).

Data extraction

Data about publication (First author's last name, year of publication), country, number of cases with GDM and normal pregnant women (NPW), gestational ages at the time of evaluation, and mean ± standard deviation (SD) of serum Se concentration in both GDM and NPW groups were collected. Means and SDs were represented in microgram per litter (μg/L) for all studies except for study of Bo et al. [13] in which the data were reported as μmol/L. We tried to convert all measurements in the study of BO et al. [13] to μg/L, but the results were incomparable; therefore, we decided to use the intact mentioned values. Two authors separately extracted the data (TJ and AAF) and discrepancies were resolved by debate with a third author (ASA).

Statistical methods

Mean serum selenium levels and its standard deviation (SD) for participants in GDM and NPW was used to calculate the bias corrected standardized mean difference (Hedges' *g*) [17] which was considered as effect size. Summary Hedges' *g* with its corresponding 95% confidence interval (CI) was derived by using random effects model [18], which takes between-study variation into account. Subgroup analysis was performed to check for possible sources of heterogeneity and between subgroup heterogeneity. Data, effect estimates, and results of the meta-analyses were illustrated as forest plots. The forest plot displays effect estimates and confidence intervals for both individual studies and meta-analysis. Each study is represented by a block at the point estimate of intervention effect with a horizontal line extending either side of the block [19].

To assess whether the observed differences in results is by chance, Cochrane *Q* test (which is a chi-squared test) was used; and $P < 0.05$ provides evidence of heterogeneity among the studies [19,20]. The degree of heterogeneity was quantified using I^2 index:

$$I^2 = \left[\frac{(Q - df)}{Q}\right] \times 100$$

Q is the chi-squared statistic and *df* is its degrees of freedom. I^2 values range between 0 and 100%, and I^2 values of 25, 50 and 75% are referred to as low, moderate, and high estimates, respectively [20].

Sensitivity analysis was also used to explore the extent to which the overall effects depend on a particular study or group of publications. Publication bias was assessed by visual inspection of Begg's funnel plots, which are simple scatter plots of the intervention effect estimates from individual studies against some measure of each study's size or precision [21]. Formal statistical assessment of funnel plot asymmetry was also incorporated with Egger's regression asymmetry test and Begg's adjusted rank correlation test [22]. Stratified meta-analysis was used to assess the association between serum Se concentration and gestational diabetes mellitus in different gestational ages. In stratified meta-analysis, studies are classifies on the basis of a moderator variable; then the effect size is compared within each subgroup, separately [19,20]. Statistical analyses were carried out by the use of Stata software version 11.2 (Stata Corp, College Station, TX, USA). *P* values less than 0.05 were considered as statistically significant.

Results

We found 1092 studies through our systematic search. We excluded 620 studies with irrelevant topics, and also 368 articles in animal models. From the 104 remained articles, 97 studies were excluded because those studies had evaluated maternal-fetal status of several trace elements other than Se. Among the 7 related studies, one study had evaluated changes in serum Se concentration during the gestational period in glucose-intolerant subjects [23], thereby it was mentioned in systematic review but not in meta-analysis. Finally, we found 6 articles to conduct the meta-analysis. Fig. 1 shows the process.

Essential characteristics of studies enrolled in meta-analysis are shown in Table 1. In summary, from 723 pregnant women ≥ 18 years participated in 7 studies, 701 subjects had been involved in 5 case control studies [11–13,15,16] and one cross-sectional study [14]. In one study, 22 pregnant women had been followed during their gestational period to evaluate the relation between gestational age and serum Se concentration [23]. Al-Saleh et al. [16] had evaluated only obese pregnant women (BMI > 30 kg/m^2); however, in the other studies participants had been distributed from normal to overweight or even obese. Measurement of serum Se concentration had been performed at the time of delivery in 2 studies

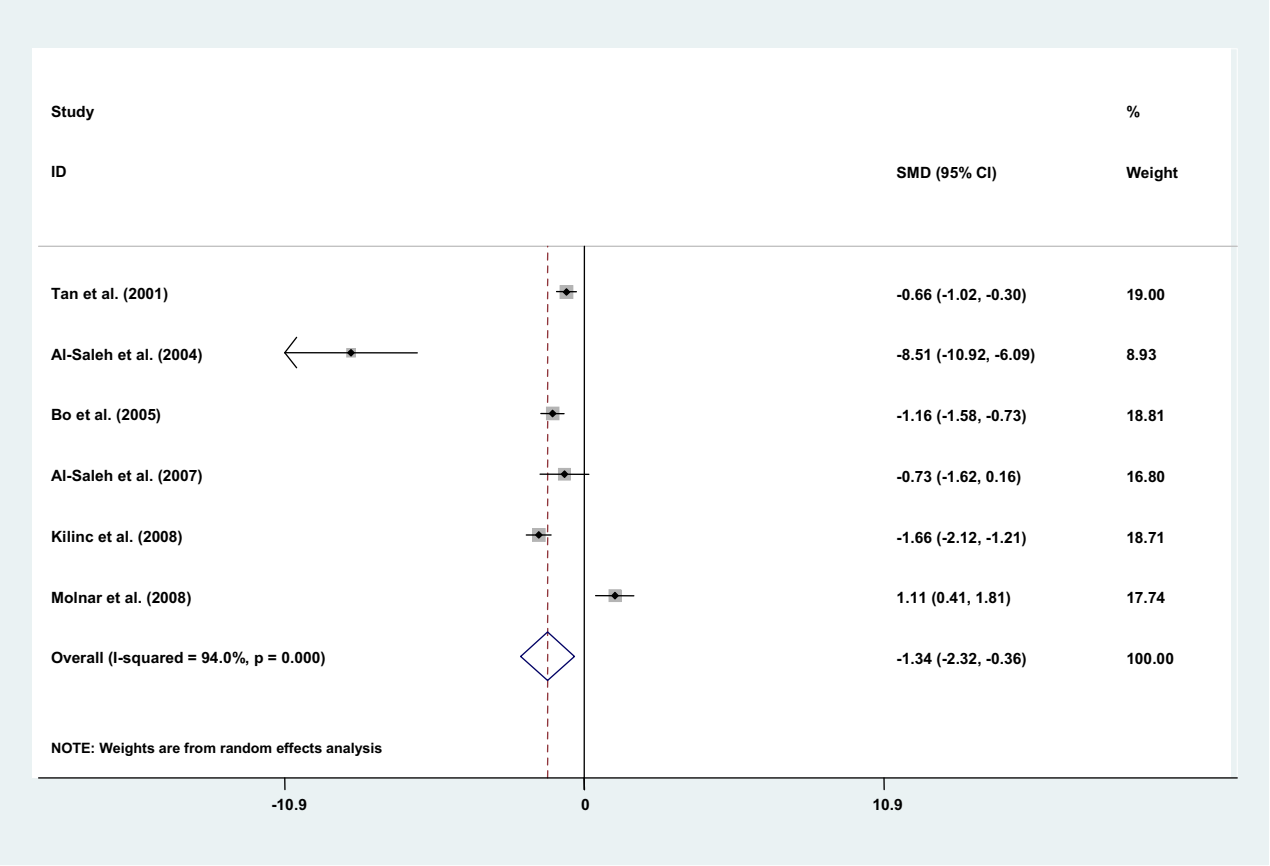

Fig. 2. Forest plot of the association between serum Se concentration and GDM.

[12,16] while in 3 studies it had been performed during 24–28 or 30 weeks of pregnancy when oral glucose tolerance tests (OGTTs) were done routinely [13–15]. Tan et al. assessed the Se concentration in 2 periods; first, during 20–33 weeks and second, between 33 and 42 weeks of gestational period [11]. In the study conducted by Hawkes et al. participants were checked between 12 and 34 weeks of pregnancy [23].

Assessment of Se status

Selenium had been measured by graphite furnace atomic absorption spectrophotometry in 4 studies [12–14,16] while Tan et al. and Molnar et al. used hydride generation atomic fluorescence spectrometry to report serum Se concentration [11,15]. In one study, authors used high-performance liquid chromatographic-fluorescence method for determination of serum Se concentrations [23]. Four studies [12,14,16,23] stated that the used methods were validated, but the validation procedure and required data were not demonstrated. Tan et al. [11] used the reference materials of cattle serum and human hair, while Molnar et al. [15] used a human reference serum for methods validation; and only stated that the accuracy and precision of their methods were acceptable. Bo et al. [13] validated the used method by a normal human reference serum. The authors did not demonstrate the results of validation study; and only stated that the analytical procedures were reliable and the coefficients of variation were 5.6–7.6%.

Assessment of gestational diabetes mellitus

Almost all studies mentioned that the OGTTs had been performed on pregnant women according to standard criterion between 24 and 28 weeks of pregnancy. At first a 50-g OGTT was performed. If the 1-h postprandial serum glucose concentration was greater than or equal to 140 mg/dL, it was followed by a 3-h 100-g OGTT. Blood samples were collected after 12 h of fasting and at 60, 120, and 180 min after glucose ingestion. If two or more of the following plasma values exceeded the mentioned values, it was diagnosed as gestational hyperglycemia: 95 mg/dL for fasting, 180 mg/dL for 1-h, 155 mg/dL for 2-h, and 140 mg/dL for 3-h after glucose ingestion [24]. Molnar et al. [15] used 75-g OGTT according to World Health Organization Guidelines [25].

The association between serum Se concentration and GDM

The overall data from 6 studies (containing 147 women with GDM and 360 normoglycemic pregnant women) demonstrated that serum Se concentration is lower in women with gestational hyperglycemia compared to normoglycemic pregnant women (Fig. 2: Hedges = −1.34; 95% CI: −2.33 to −0.36; $P < 0.01$). The chi-squared test for heterogeneity was significant ($P \leq 0.001$) and I^2 was 94.0%. Considering Fig. 2, the inconsistency might be due to the studies of Al-Saleh et al. and Molnar et al. [12,15]; but heterogeneity still existed after excluding of mentioned studies in meta-analysis (Fig. 3: $P < 0.01$, and $I^2 = 75.6\%$). The study team decided to conduct a stratified meta-analysis according to gestational age at the time of serum Se assessment. Three studies with 184 participants assessed Se status in third trimester or at delivery [11,12,16], while 4 studies with 417 participants had data on serum Se concentration in second trimester [11,13–15]. Tan et al. assessed serum Se status both in second and third trimesters [11]. Stratified meta-analysis showed that concentration of Se in the sera of women with GDM was lower than normal pregnant women both in second and third

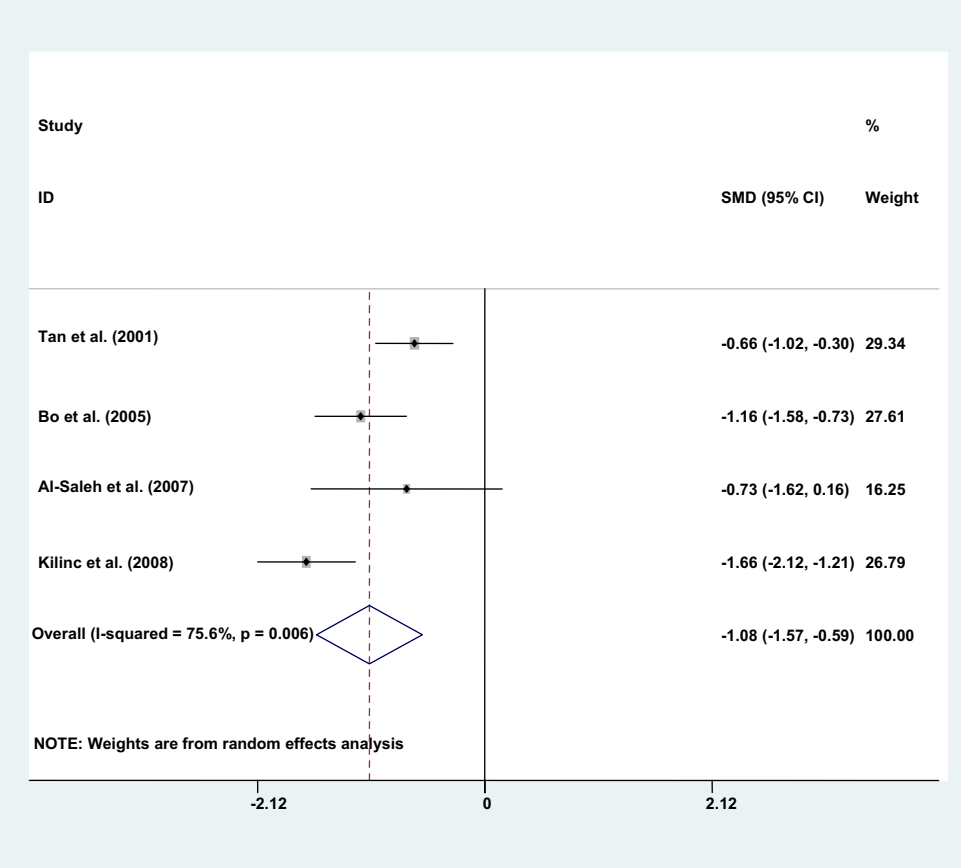

Fig. 3. Forest plot of the association between serum Se concentration and GDM after the extraction of 2 studies.

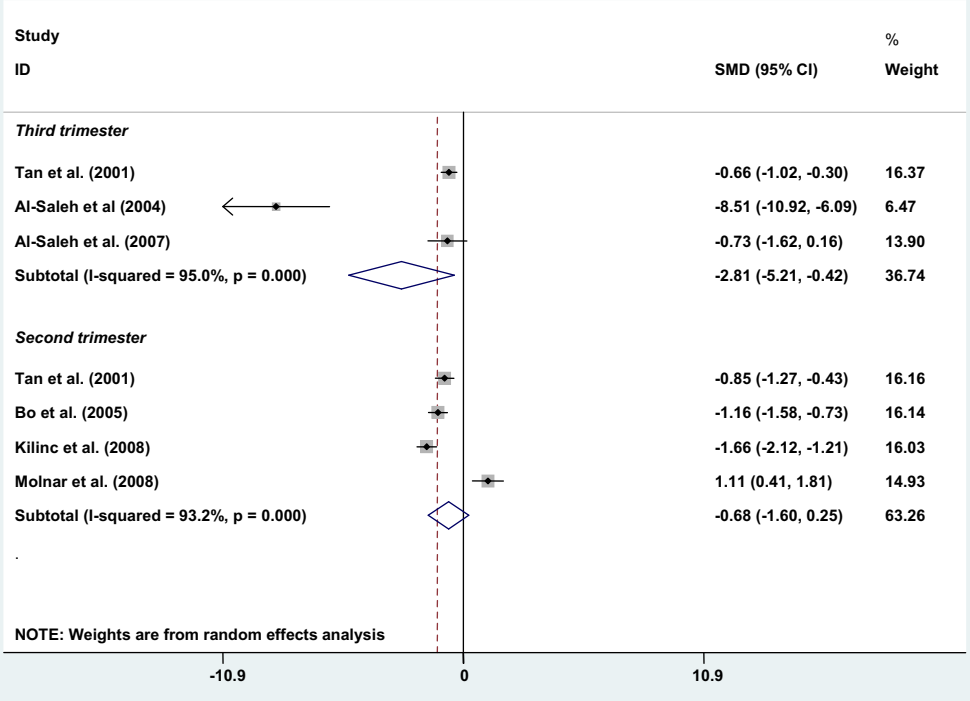

Fig. 4. Forest plot of the association between serum Se concentration and GDM in each trimester.

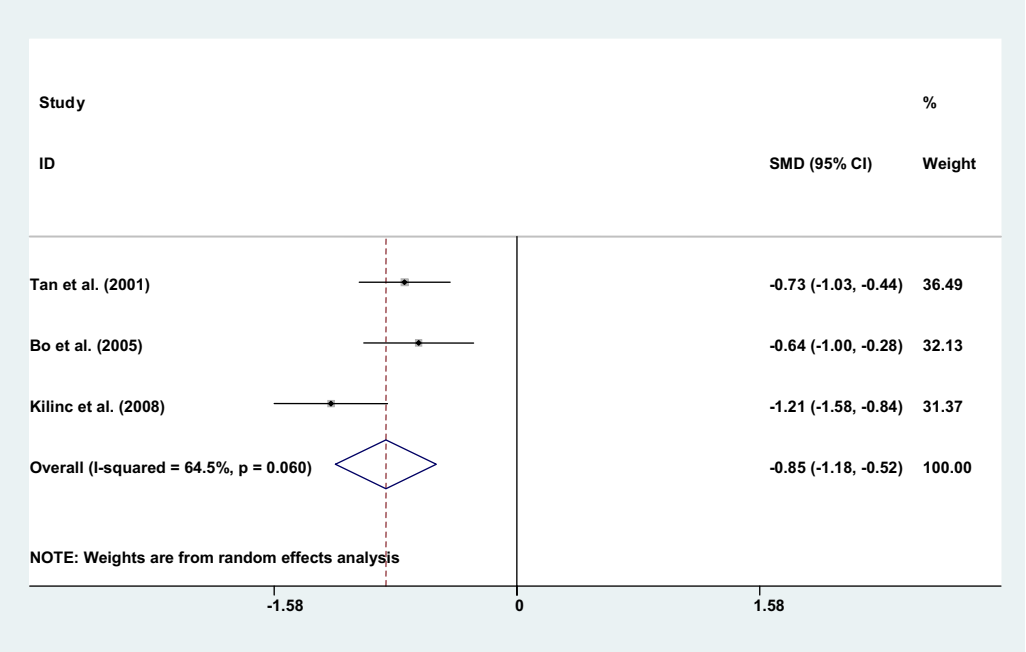

Fig. 5. Forest plot of the association between serum Se concentration and IGT.

trimesters, but the result was not significant in second trimester (Fig. 4; second trimester: Hedges = −0.68; 95% CI: −1.60–0.25; $P = 0.15$, third trimester: Hedges = −2.81; 95% CI: −5.21 to −0.42; $P < 0.05$). The chi-squared test and I^2 represented heterogeneity among the studies in each subgroup (Fig. 4; second trimester: $P < 0.001$ and I^2 was 93.2%; third trimester: $P < 0.001$ and I^2 was 95.0%).

The association between serum Se concentration and impaired glucose tolerance

Serum Se status had been compared in 3 studies containing 189 pregnant women with IGT and 314 normoglycemic pregnant women [11,13,14]. The overall data represented that serum Se status is lower among those with IGT (Fig. 5: Hedges = −0.85; 95% CI: −1.18 to −0.52). The chi-squared test and I^2 denoted that there was heterogeneity among the studies ($P = 0.06$, and I^2 was 64.5%).

In spite of a brief asymmetry observed in Begg's funnel plot, the Egger's test demonstrated that there is no evidence of publication bias ($P = 0.54$).

Discussion

Several evidences indicate that serum selenium level decreases during pregnancy [26–28]. The probable reasons could be hemodilutional phenomenon in pregnancy, increased fetal requirement, and deposition in placenta [11,14,15]. In addition, due to increase of lipid peroxidation during pregnancy, the activity of antioxidants like glutathione and erythrocyte glutathione peroxidase increases; hence the level of serum Se decreases particularly in third trimester [3]. Women with GDM or IGT are more susceptible to oxidative stress conditions due to hyperglycemic status and insulin resistance. Therefore, the need for more Se is evident in such patients. On the other hand, Se as an insulinomimetic element can have beneficial effects in GDM. Bo et al. [13] showed that serum Se concentration is negatively associated with gestational hyperglycemia (odds ratio = 0.92, 95% CI: 0.87–0.95, $P \leq 0.0001$). Four of 6 studies enrolled in our meta-analysis had confirmed that serum Se concentration is lower in women with GDM compared to normal pregnant women [11–14]. The result in one study was not significant [16] and Molnar et al. [15] reported inconsistent data. The overall data demonstrated that serum Se concentration is significantly lower in pregnant women with gestational hyperglycemia comparing to normal pregnant women (Fig. 2). Regarding the inverse correlation between level of Se and obesity [14], the non-significant result in the study of Al-Saleh et al. [16] might be due to diversity in BMI of cases and controls; the subjects were obese and BMI in cases was significantly lower than BMI in control group ($P \leq 0.05$). Molnar et al. stated that because of the lack of sufficient data on plasma Se concentration of GDM cases, it was not possible to reach a distinct conclusion [15].

Stratified meta-analysis demonstrated that serum Se concentration is lower in women with GDM both in second and third trimesters; however the results were significant after the 33th week of pregnancy period. The reduction of Se levels at the end of third trimester is more than the reduction in second trimester (Fig. 4). This result must be due to higher tendency of insulin resistance and also higher activity of peroxidase enzymes in third trimester. Fig. 5 shows that serum Se concentration is lower in women with IGT; this could be due to the effects of Se on glucose tolerant mechanisms [13]. We found significant negative correlation between serum Se values and GDM prominent in the third trimester. But we could not indicate a causal relationship between Se and GDM due to the design of the studies (case–control or cross sectional) enrolled in this meta-analysis. Moreover, it is still unknown whether reduction in serum Se concentration is a predisposing factor for GDM and IGT, or pregnant women with hyperglycemic status have low serum Se levels. Cohort studies in different populations are recommended to clarify the causality. The other limitations of our study are as follows: (*i*) heterogeneity in age, weight, and inflammatory status of the patients in studies, which may affect serum Se concentration; and (*ii*) geographical diversity of Se concentration in the soil that influences the dietary Se intake among the populations and its unclear effect on serum Se concentration. More precise investigations with the large populations are required to overcome the problems and reach to exact conclusions about the role of Se supplementation in pregnant women with GDM or IGT.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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