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Review

Sex hormone binding globulin for prediction of gestational diabetes mellitus in pre-conception and pregnancy: A systematic review

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ABSTRACT

Aim: The purpose of the present study was to assess the relationship of sex hormone binding globulin (SHBG) and gestational diabetes mellitus (GDM).

Methods: The Cochrane Library, Medline, ScienceDirect, and Web of Science were searched for studies published from the inception of the databases up to February 2019. Our inclusion criteria were published observational full-text articles. All data were analyzed using Review Manager 5.3. Of 208 papers reviewed, 26 studies (n = 6668) were considered for meta-analysis.

Results: The SHBG level was significantly lower in women with GDM compared to healthy women (MD = −11.86; 95% CI: [−13.02, −10.71]). Also, SHBG in women with PCOS and GDM and obesity was significantly lower than women with PCOS without GDM (MD = −38.14; 95% CI: [−56.79, −19.48]) and normal weight women (MD: −58.96; 95% CI: [−79.32, −38.59]). SHBG in the second trimester was lower than that in the first trimester and pre-conception.

Conclusions: This systematic review showed that the level of SHBG is significantly lower in GDM pregnant women than that in healthy women. The results of this systematic review about the relationship of GDM and SHBG and suggestion to assess this marker in early pregnancy should be considered with caution.

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Contents

1. Introduction

Gestational diabetes mellitus (GDM) affects approximately 1–24% of pregnancies [1]. It is defined as glucose intolerance that is recognized for the first time during pregnancy [2]. GDM is associated with adverse complications for the mother (pre-eclampsia, cesarean section) and the fetus (dystocia, large for gestational age, and macrosomia) [3–5]. Early prediction of GDM can lead to appropriate interventions such as lifestyle changes or pharmacological means to reduce adverse health impact. There is no standard agreed-upon screening protocol for GDM. Most institutions use risk factors or universal screening to diagnose patients at risk for GDM [6]. Predisposing factors for developing GDM are as follows: previous history of GDM, previously elevated blood glucose level, ethnicity (i.e. South and Southeast Asian, Aboriginal, Pacific Islander, Maori, Middle Eastern, and African), age $\geq$ 40 years, family history of diabetes mellitus, obesity, body mass index greater than 35 kg/m^2, previous macrosomia, polycystic ovarian syndrome, medications such as corticosteroids and antipsychotics, and abnormal pregnancy weight gain [6,7].

The diagnosing method for GDM that is recommended by the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) and World Health Organization (WHO) is the two-hour tolerance test after consuming 75 g oral glucose (OGTT) [8–10]. The National Institutes of Health (NIH) recommendation is the three-hour glucose test after consuming 100 g OGTT[10].

Considering the importance of early detection, many studies have been conducted on analyzing biomarkers either alone or in conjunction with other risk factors as predictive tools for detecting GDM [6]. Some of these biomarkers include cytokines, adipocytokines, naturetic peptides (ANP, BNP and CNP), glycemic markers (fasting glucose, post-load glucose, fasting plasma insulin (FPI), HbA1c), inflammatory markers (C-reactive protein, tumor necrosis factor-alpha), adipocyte-derived markers (adiponectin, leptin), placenta-derived markers (follistatin-like-3, placental growth factor), and others (e.g., glycosylated fibronectin, soluble (pro) renin receptor, alanine aminotransferase, serum ferritin and iron levels, and insulin resistance markers [fasting insulin, sex hormone-binding globulin]) [6–11].

Among these markers, sex-hormone binding globulin (SHBG) levels in the first trimester has been suggested as a valuable screening test for GDM [12]. SHBG is a protein made by the liver; its production is controlled by insulin and is inversely related to insulin resistance [13]. SHBG plays an important role in regulating and transferring sex hormones [14]. Estradiol stimulates the synthesis of SHBG while testosterone and insulin decrease it [14–16]. The high estrogen level during pregnancy increases the SHBG level up to 24 weeks of gestation. At that time, the level stabilizes and may play a role in hyper-insulinemia and insulin resistance that increase progressively from the late second trimester [17–19]. Scientific evidence regarding the relationship of SHBG with GDM is increasing; however, the mechanism of the relationship is not fully understood [18]. In

this regard, some studies reported that women with GDM showed lower concentrations of SHBG compared to healthy pregnant women, while McElduff et al. found the contrary [20]. The potential causes of these conflicting results were poorly described.

To the best of our knowledge, there is no systematic review on prediction of gestational diabetes using SHBG measurement. Moreover, the literature is inconsistent about the relationship of SHBG with gestational diabetes. Therefore, the purpose of our review was to study the relationship between SHBG and gestational diabetes in pre-conception and pregnancy.

2. Methods

This review followed the methodology consistent with Systematic Reviews and Meta-Analyses of Observational Studies. We utilized the checklist of Downs and Black (1998) for quality assessment [21]. The protocol of this systematic review was registered in PROSPERO with the reference number CRD42018108841.

2.1. Search strategies

We searched for published studies in Medline (21May 2018), Science Direct (25 May 2018), Cochrane (25 May 2018) and Web of Science (30 May 2018). The search was updated up to February 2019.

2.2. Inclusion and exclusion criteria

We used the following inclusion criteria: a) full-text articles published in any languages, b) observational studies such as case-control, cohort, nested case-control, and prospective cross-sectional studies, and c) the diagnosis of gestational diabetes was confirmed by an oral glucose tolerance test (OGTT) with different types of criteria. Overweight and obese women (BMI $\geq$ 24) and women with a history of polycystic ovarian syndrome were included in this review and analyzed as a subgroup.

Studies on type 1 or 2 diabetes or pre-gestational diabetes, maternal chronic disease, animal studies and cross-sectional studies were excluded from this review. In addition, studies with no clear statement about the diagnosis of GDM, or with no data on exposure and outcome were excluded.

2.3. Study selection and data extraction

The search was carried out by MZ and SFS. Two authors (SFS and JMN) independently screened all searched studies and extracted data using the Covidence software from those articles that were included in the review. If there was a conflict, it was resolved by discussion. If the problem was not resolved, the conflict was resolved by a third party (SJ or PA). For data extraction, we adopted a form recommended by the Cochrane Non-Randomized Studies Methods Group. Two investigators independently extracted information on participant characteristics, measurements of SHBG and outcomes, and potential confounders.

2.4. Appraisal of methodological quality of primary studies

All articles meeting the eligibility criteria were assessed for their methodological quality using the checklist of Downs and Black (1998) by two investigators (SFS and PA). The following areas were covered using twenty-seven questions: ten questions for assessing reporting bias, three questions for assessing external validity, seven questions for evaluating internal validity, six questions for assessing (selection bias) and one question for assessing the power of the study [21]. The total quality score was classified as follows: <14 = poor, 15–19 = fair and >20 = good [22].

2.5. Statistical analysis

Mean differences (MD) and 95% confidence intervals (95% CI) were calculated to assess the differences in serum SHBG between groups. In seven studies, medians and IQRs were used, which were converted into mean and standard deviation [23–28]. The significance level was determined according to the Z test. Forest plots were used to demonstrate effect sizes and 95%CI. Heterogeneity among the included studies was assessed by I^2 statistics. By default, we used a fixed effects model for all pooled studies. According to the primary results of heterogeneity, if $I^2 > 40\%$, a random effects model was used. We also conducted a sensitivity analysis to explore the potential sources of heterogeneity if heterogeneity across studies was statistically significant. Sensitivity analyses were carried out by sequentially omitting one single study each time to test the robustness of uncertainty in the meta-analysis. All data were analyzed with Review Manager (RevMan 5.3), a statistical software provided by the Cochrane Collaboration. The significance level was set as 0.05.

3. Results

3.1. Literature search

A flow diagram of the included and excluded studies is shown in Fig. 1. The database searches identified 459 records. After removing the duplicates (n = 251), two reviewers (SFS and JMN) screened the titles and abstracts for potentially relevant studies (n = 208) independently. Thirty-six full-text articles were considered as eligible. For two articles, we contacted the authors in order to obtain primary data. These two studies were excluded due to a lack of information [29,30]. Eight studies were excluded because of wrong outcomes or study design, and 26 studies were included in the meta-analysis.

3.2. Characteristics and quality assessment of study

The included studies were published from 2000 to February 2019 and had a case-control (n = 12), prospective cohort (n = 13) or prospective cross-sectional design (n = 1). The studies included a total of 6668 participants: 1894 women diagnosed with GDM, and 4774 healthy pregnant women). The characteristics of the studies included in the meta-analysis are shown in Table 1.

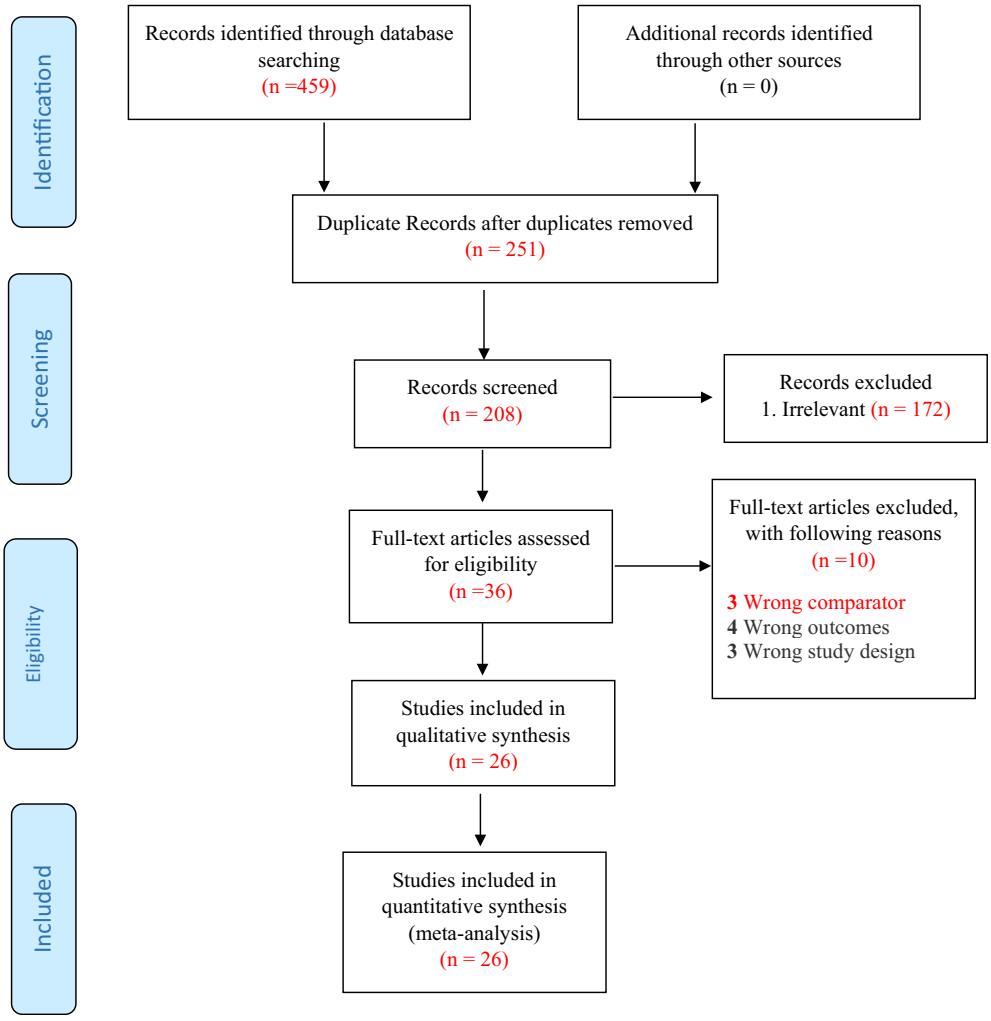


Fig. 1 – Flow diagram of the study.

Of 26 included studies, three were conducted in China [31–33], three in the Netherlands [24–28], two in Austria 30–34], two in the United Kingdom [31–35], two in Canada [36–37] four in the USA [12,37,38,41,47] and two in Turkey [45,46]. Other studies were conducted in the Spain [39], Romania [40], Egypt [42], Saudi Arabia [18], Poland [43], Finland [44], and Iran [48]. The sample size of these studies ranged from 14 to 678. Six of the included studies recruited women with PCOS and GDM [24,25,28,31,32,48], and nine recruited women with GDM and BMI > 24 [12,18,23,26,34–36,39]. Blood samples for measuring SHBG were collected in the preconception period in seven studies [24,25,28,32,41,47,48], in the first trimester of pregnancy in 10 studies [12,23,25,26,31,33,37,38,42,45] and in the second trimester in seven studies [12,18,25,27,34–36,39]. The following guidelines were used for diagnosis of gestational diabetes: The International Association of the Diabetes and Pregnancy Study Groups [18,32,33,35], American Diabetes Association [24,25,31,37,42,47], Canadian Diabetes Association [27,36], German Diabetes Association [34], Australasian Diabetes in Pregnancy Society [23], ACOG [12,41,44–46], WHO [26,40], Carpenter- Coustan criteria [38,47], the Spain National Diabetes Data Group [39], and the Polish Gynecology Society Recommendation [43]. One study did not mention any guidelines for GDM diagnosis [28]. The quality assessment of the included studies is shown in table 2. The median total quality score was 15, which has a fair quality according to the Kennelly et al's recommendation [22].

3.3. *Overall meta-analysis*

As indicated in Fig. 2, there were 1,894 participants in case groups and 4,774 in control groups. The overall level of serum SHBG in GDM patients was significantly lower than that in the healthy controls (MD = −11.86; 95% CI: [−13.02, −10.71], $P < 0.00001$). Initially we used a fixed effects model for calculating MDs, but with the high level of heterogeneity ($P < 0.00001$, $I^2 = 97\%$), we considered sensitivity analysis and random effects. Sensitivity analysis was carried out by omitting studies one by one to explore potential sources of heterogeneity. We then assessed relevant changes in the pooled results using random effect analysis (Fig. 3) [25,31,33,36,40–42,44,46]. By eliminating 10 papers in order through the sensitivity analysis, the rate of heterogeneity reduced to 46% ($I^2 = 46\%$, $P = 0.03$). However, the level of SHBG in GDM

Table 1 – Characteristics of studies included in the systematic review.

Study	Location	Study type	Sample	Method	GDM criteria	Case group		Control group		SHBG measurement trimester
						Sample size	SHBG	Sample size	SHBG	
Abell, 2017	Australia	Cohort study	Serum	Demeditec Diagnostics ELISA (DE2996)	ADIPS 1998	25	329.98 ± 240.73	78	355.67 ± 248.9	1st trimester (12–15 wks)
Badon, 2018	Oakland	Nested case-control study	Serum	ELISA	Carpenter-Coustan criteria	256	57.7 ± 45.1	497	79.7 ± 58.5	Pre-conception
Bartha, 2000	Spain	Case-control study	Serum	Radio-immuno-assay	National Diabetes Data Group	34	309.54 ± 112.22	32	460.54 ± 144.43	2nd trimester (24–28 wks)
Berggren, 2017	USA	Retrospective cohort study	Serum	Hemiluminescent immunometric assay (IMMULITE 2000)	Carpenter-Coustan criteria	14	228 ± 72	231	288 ± 93	1st trimester (11–14 wks)
Bogdan, 2017	Romania	Case-control study	Serum	–	WHO	50	78.57 ± 45.58	50	88.9 ± 53.11	Early 2nd trimester (14–17 wks)
Caglar, 2012	Turkey	Prospective cross-sectional study	Serum	RIA	ACOG	30	97.8 ± 2.9	63	99.9 ± 3.6	Early 2nd trimester (13–16 wks)
de Wilde, 2015	Netherlands	Prospective cohort study	Serum	Electrochemilu-minescence immunoassay on the Modular E170	American Diabetes Association (2003)	22 22 22	197.5 ± 167.6 320.5 ± 256.96 40.5 ± 28.26	50 50 50	267 ± 206.85 400 ± 311.66 63.5 ± 40.3	1st trimester (10–12 wks) 2nd trimester (24–28 wks) Pre-pregnancy
de Wilde, 2014	Netherlands	Prospective cohort study	Serum	Electrochemilu-minescence immunoassay on the Modular E170	American Diabetes Association (2003)	41	38 ± 27.77	148	58 ± 46.3	Pre-pregnancy
Hedderson, 2014	Oakland, CA	Case-control study	Serum	ELISA	ACOG	226	57.7 ± 45.1	407	79.7 ± 58.5	Pre-pregnancy
Kopp, 2001	Vienna, Austria	Case-control study	Serum	ELISA	German Diabetes Association	42	512 ± 249	48	643 ± 137	2nd trimester (20–30 wks)
Kumru, 2016	Turkey	Prospective cohort study	Serum	Chemiluminescent immunometric assay	ACOG	38	195.7 ± 97.7	295	281.3 ± 92.6	1st trimester (6–14 wks)
Li, 2018	Beijing, China	Prospective cohort study	Serum	ELISA	ADA	75	207.2 ± 12.74	173	255.3 ± 8.86	1st trimester before 15th wk)
Maged, 2014	Egypt	Prospective cohort study	Serum	ELISA	ADA	27	191.07 ± 24.11	242	210.75 ± 28.21	1st trimester
Mehrabian, 2013	Iran	Prospective cohort study	Serum	Modular E 170	ADA	50	44.4 ± 14.8	130	63.5 ± 22.7	Pre-pregnancy
Migda, 2016	Poland	Prospective cohort study	Serum	ELISA	Polish Gynecology Society Recommend	19	249 ± 100.3	135	338.4 ± 92	1st trimester (11–14 wks)
Morisset, 2011	Canada	Case-control study	Serum	Radio-immuno- assay	CDA	20	178.6 ± 30.7	27	194.6 ± 36	2nd trimester (26 ± 3.7 wks
Nanda, 2011	London, UK	Case-control study	Serum	DELFIA	WHO	80	224.5 ± 166.66	300	295.9 ± 223.44	1st trimester (11–13 wks)
Rasanen, 2013	Finland	Case-control study	Serum	Enzyme-linked immunoassays	ACOG	90	84 ± 46	92	91 ± 66	1st trimester (5–13 wks)
Smirnakis, 2007	Boston, MA	Nested Case-control study	Serum	Immunometric assay (Diagnostic Products Corporation, Los Angeles, CA	ACOG	35 35	185.1 ± 105.1 284.8 ± 92.7	73 73	255.6 ± 92.1 320 ± 74.5	1st trimester (11 wks) 2nd trimester (24–28 wks)
Tawfeek, 2017	Saudi Arabia	Case-control study	Serum	ELISA	IADPSG	45	23 ± 24.44	45	78 ± 59.6	2nd trimester (24–28 wks)
Thadhani, 2003	Boston, MA	Nested Case-control study	Serum	Immunometric assay	ADA	44	187 ± 82	94	233 ± 92	1st trimester
Thériault, 2016	Canada	Nested Case-control study	Serum	Electro-chemiluminescene immunoassay	CDA	264	357 ± 118.5	528	411 ± 130.37	2nd trimester (14–17 wks)
Veltman-Verhulst, 2010	Netherlands	Prospective cohort study	Serum	Modular E170	–	21	40 ± 34.4	29	63 ± 77.8	Pre-pregnancy
White, 2016	London, UK	Prospective cohort study	Serum	–	IADPSG	275	386.7 ± 109.9	678	437.2 ± 127.8	2nd trimester (17 wks)
Xia, 2017	China	Prospective cohort study	Serum	Modular E170	IADPSG	31	41.5 ± 37.5	63	123.7 ± 95.7	Pre-pregnancy
Zhang, 2018	China	Prospective cohort study	Serum	Immune-radiometric assay	IADPSG	40	93.9 ± 34.4	266	128.1 ± 60.3	1st trimester

Table 2 – Quality assessment of the articles reviewed.

Study ID (Author, Year)	Clarity	External validity	Internal validity		Power	Total score
			Bias	Confounding		
Abell, 2017	8	0	3	3	1	15
Badon, 2018	10	3	4	4	1	22
Bartha, 2000	8	0	3	2	0	13
Berggren, 2017	7	0	3	3	1	14
Bogdan, 2017	8	0	3	3	0	14
Caglar, 2012	8	0	3	3	1	15
de Wilde, 2015	9	0	3	3	0	15
de Wilde, 2014	9	0	3	3	0	15
Hedderson, 2014	9	3	3	4	1	20
Kopp, 2001	8	0	3	2	1	14
Kumru, 2016	8	0	3	3	1	15
Li, 2018	8	0	3	2	1	14
Maged, 2014	7	0	3	3	0	13
Mehrabian, 2013	7	0	3	4	0	14
Migda, 2016	8	0	3	2	1	14
Morisset, 2011	8	0	3	3	0	14
Nanda, 2011	9	0	3	3	0	15
Rasanen, 2013	8	0	3	4	1	16
Smirnakis, 2007	7	0	3	2	1	13
Tawfeek, 2017	8	0	3	3	1	15
Thadhani, 2003	8	0	3	2	0	13
Thériault, 2016	8	2	3	4	1	18
Veltman-Verhulst, 2010	8	0	3	3	1	15
White, 2016	9	0	3	4	0	16
Xia, 2017	8	0	3	3	0	14
Zhang, 2018	8	0	3	3	1	15
Median	8	0	3	3	1	15

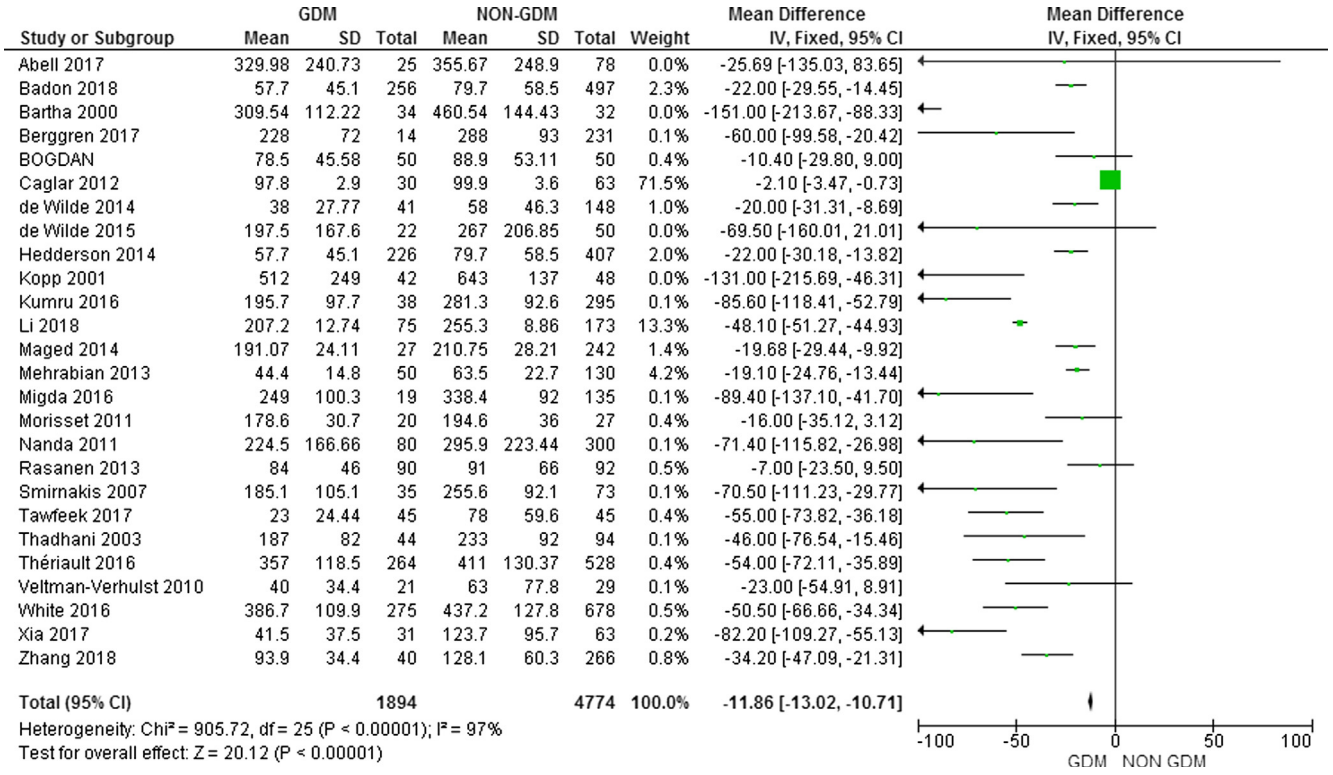


Fig. 2 – Forest plot of SHBG level in GDM and healthy pregnant women using fixed effect.

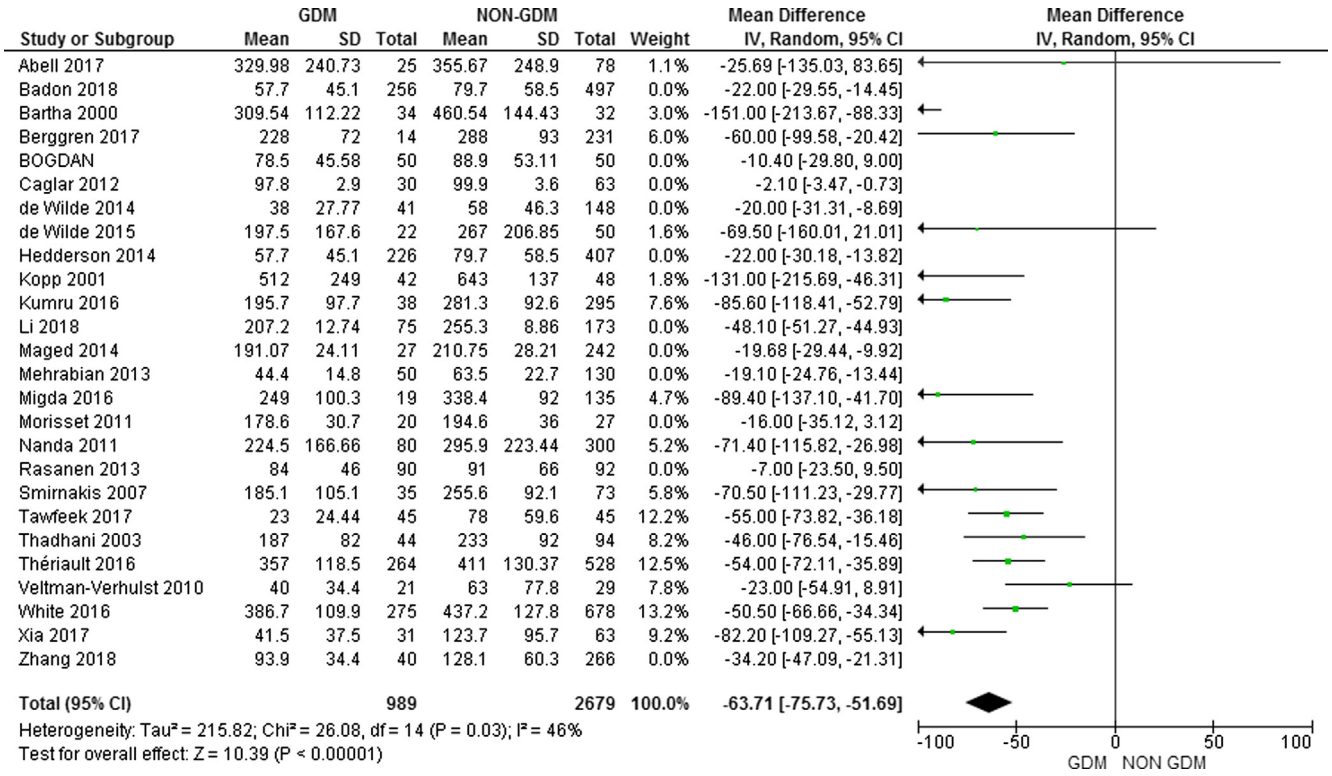


Fig. 3 – Forest plot of Sensitivity analysis by omitting studies to explore potential sources of heterogeneity.

pregnant women was still significantly lower than that in the control group (MD: −63.71, 95% CI: [−75.73, −51.69], P < 0.00001). Funnel plots are shown in Fig. 4(A) and (B).

3.4. *Subgroup analysis*

In this review, the subgroup analysis was used for those studies that studied women with PCOS or BMI ≥ 24, and used different trimesters for measuring SHBG.

3.4.1. *PCOS subgroup analysis*

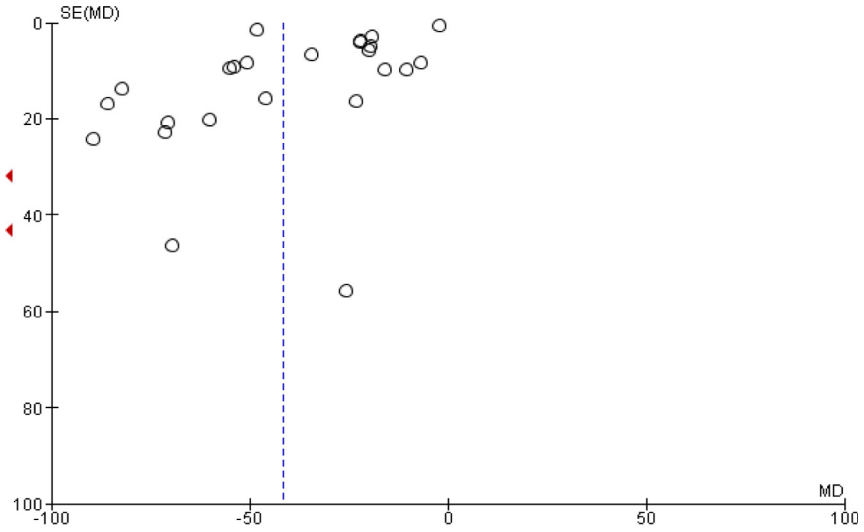
The results from the analysis of SHBG in women with PCOS who either had or did not have GDM are shown in Fig. 5. There were 240 participants in the case groups and 593 participants in the control groups. It is apparent from Fig. 5 that the overall level of SHBG in PCOS women with GDM was significantly lower than that in PCOS women without GDM (MD = −38.14; 95% CI: [−56.79, −19.48], P < 0.0001). Because of the high level of heterogeneity (P < 0.00001; I^2 = 95%), the random-effect model and sensitivity analysis was used. As Fig. 6 shows, after omitting two articles [31,32], the heterogeneity was reduced to 0% (I^2 = 0%, P = 0.97) and the level of SHBG in the women with PCOS and GDM was still significantly lower than that in the women with PCOS without GDM (MD = −19.69; 95% CI: [−24.46, −14.91], P < 0.00001).

3.4.2. *Obesity subgroup analysis*

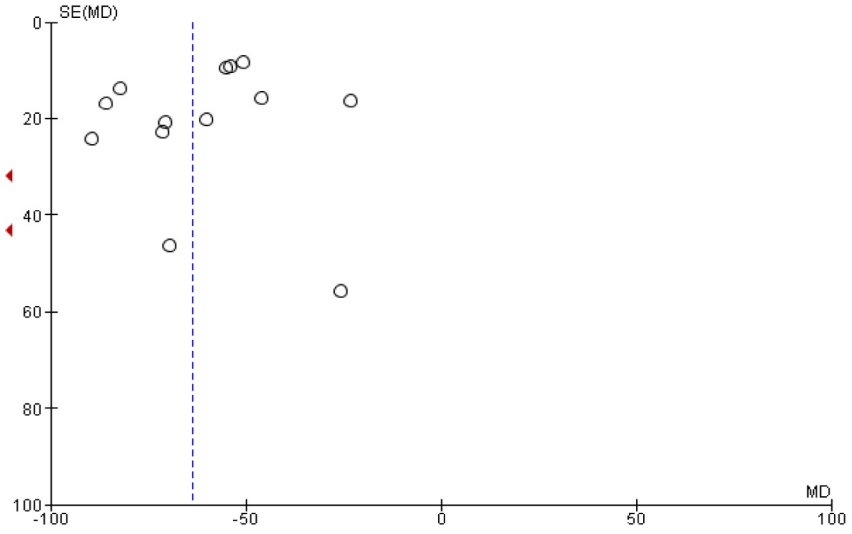
The relationship between SHBG and obesity in women with and without GDM was assessed using a pooled analysis of nine studies. The level of SHBG in obese women with GDM was significantly lower than that in obese women without GDM (MD: −58.96; 95% CI: [−79.32, −38.59], P < 0.00001). The random- effect model and sensitivity analysis were used to reduce the heterogeneity (Figs. 7 and 8). Using sensitivity analysis, the heterogeneity was reduced to 0% (I^2 = 0%, P = 0.53). After omitting 2 studies [36,37], the level of SHBG in obese women with GDM was still significantly lower than that in obese women without GDM (MD: −54.88; 95% CI: [−65.39, −44.37], P < 0.00001).

3.4.3. *Subgroup analysis based on timing of SHBG measurement*

Fig. 9 presents the subgroup analysis depending on the timing with which SHBG was measured. The random effect model was chosen because of the high level of heterogeneity in the three subgroups (pre-conception period: P < 0.003, I^2 = 70%; first trimester: P < 0.00001, I^2 = 83%; and second trimester: p < 0.00001, I^2 = 93%). There was a significant difference in SHBG level between the GDM and non-GDM groups in all three trimesters. The pooled analyses for each subgroup were as follows: pre-conception (MD = -24.94; 95% CI: [–32.72, −17.15], P < 0.00001), first trimester (MD = − 46.00; 95% CI: [−59.86, –32.15], P < 0.00001), and second trimester (MD = − 45.28; 95% CI: [−68.04, –22.52], P < 0.0001). Sensitivity analysis was used to reduce the heterogeneity in the three subgroups (Fig. 10). By omitting one study [32] in the pre-conception group (I^2 = 0%, P = 0.99), two studies [42,44] in the first trimester group (I^2 = 24%, P = 0.23) and three studies [36,39,40] in the second trimester group (I^2 = 0%, P = 0.48), the heterogeneity was reduced. The pooled analysis for different times of measurement were as follows: pre-conception (MD = -20.67; 95% CI: [−24.29, −17.05], P < 0.00001), first trime-



A: Funnel plot of SHBG level in GDM and healthy pregnant women



B:Funnel plot of Sensitivity analysis by omitting studies to explore potential sources of heterogeneity

Fig. 4 – A. Funnel plot of SHBG level in GDM and healthy pregnant women. B. Funnel plot of Sensitivity analysis by omitting studies to explore potential sources of heterogeneity.

Study or Subgroup	GDM Mean	GDM SD	GDM Total	NON GDM Mean	NON GDM SD	NON GDM Total	Weight	Mean Difference IV, Random, 95% CI
de Wilde 2014	38	27.77	41	58	46.3	148	21.3%	-20.00 [-31.31, -8.69]
de Wilde 2015	197.5	167.6	22	267	206.85	50	3.6%	-69.50 [-160.01, 21.01]
Li 2018	207.2	12.74	75	255.3	8.86	173	23.0%	-48.10 [-51.27, -44.93]
Mehrabian 2013	44.4	14.8	50	63.5	22.7	130	22.7%	-19.10 [-24.76, -13.44]
Veltman-Verhulst 2010	40	34.4	21	63	77.8	29	13.8%	-23.00 [-54.91, 8.91]
Xia 2017	41.5	37.5	31	123.7	95.7	63	15.6%	-82.20 [-109.27, -55.13]
Total (95% CI)			**240**			**593**	**100.0%**	**-38.14 [-56.79, -19.48]**

Heterogeneity: $Tau^2 = 390.96$; $Chi^2 = 100.21$, df = 5 ($P < 0.00001$); $I^2 = 95\%$
Test for overall effect: $Z = 4.01$ ($P < 0.0001$)

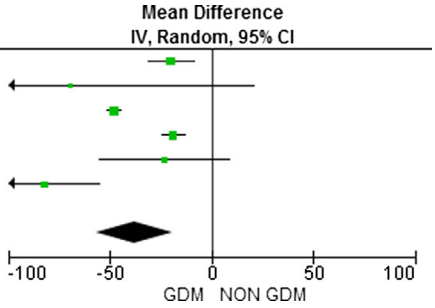


Fig. 5 – Forest plot of SHBG in PCOS women with and without GDM.

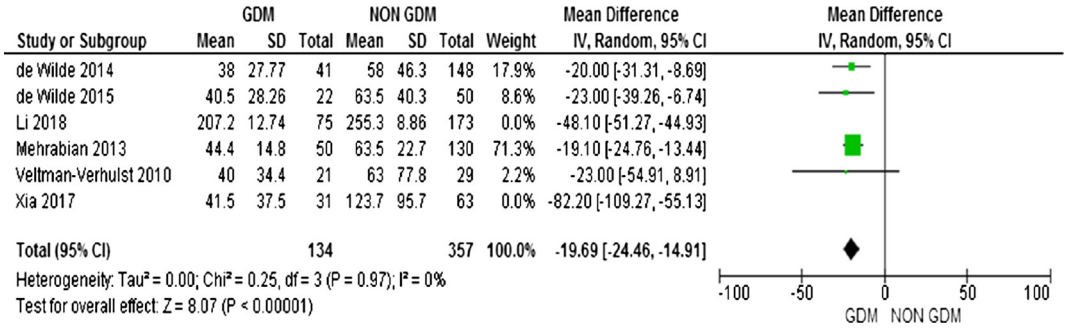


Fig. 6 – Forest plot of sensitivity analysis in PCOS women with and without GDM.

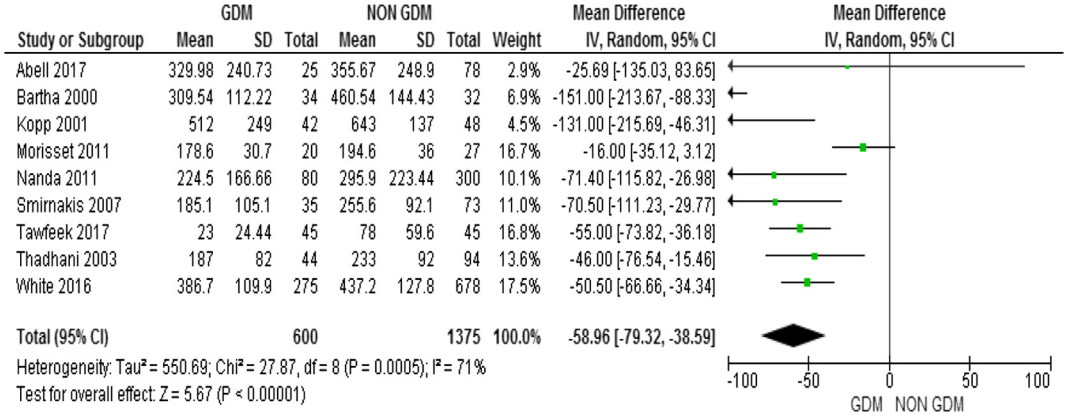


Fig. 7 – Forest plot of the SHBG level in obese women with and without GDM.

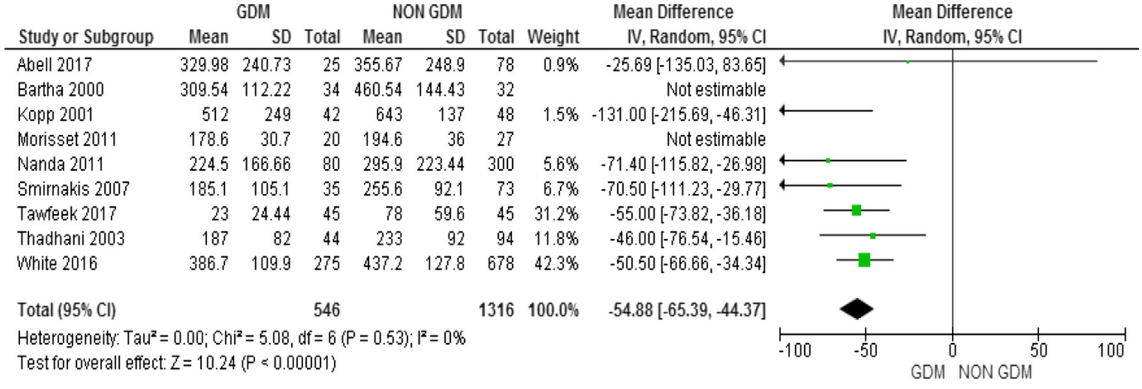


Fig. 8 – Forest plot of sensitivity analysis in obese women with and without GDM.

ster (MD = − 58. 42; 95% CI: [−70.55, −46.30], P < 0.00001), and second trimester (MD = − 52.72; 95% CI: [−62.39, −43.05], P < 0.00001). Fig. 11(A) and (B) shows the funnel plot of subgroup analysis before and after sensitivity analysis.

3.5. *Publication bias*

The Trim and Fill analysis was done for assessing the publication bias and results showed that if we account for smaller studies at the left and below part of graph, we will get a different effect measure. This means that the publication bias was existed (Supplementary Material 1)

4. Discussion

The aim of this systematic review was to evaluate the relationship between SHBG and gestational diabetes in the preconception and pregnancy periods. The results of this study showed that serum SHBG level was significantly lower in women with GDM in comparison with healthy pregnant women. Several hormones like estrogen, progestin, and insulin control plasma levels of SHBG. As well, studies show an association between SHBG and metabolism of carbohydrates. However, it is not clear which of the factors of "hyper-insuli nemia" or "insulin resistance" play a significant role in regu-

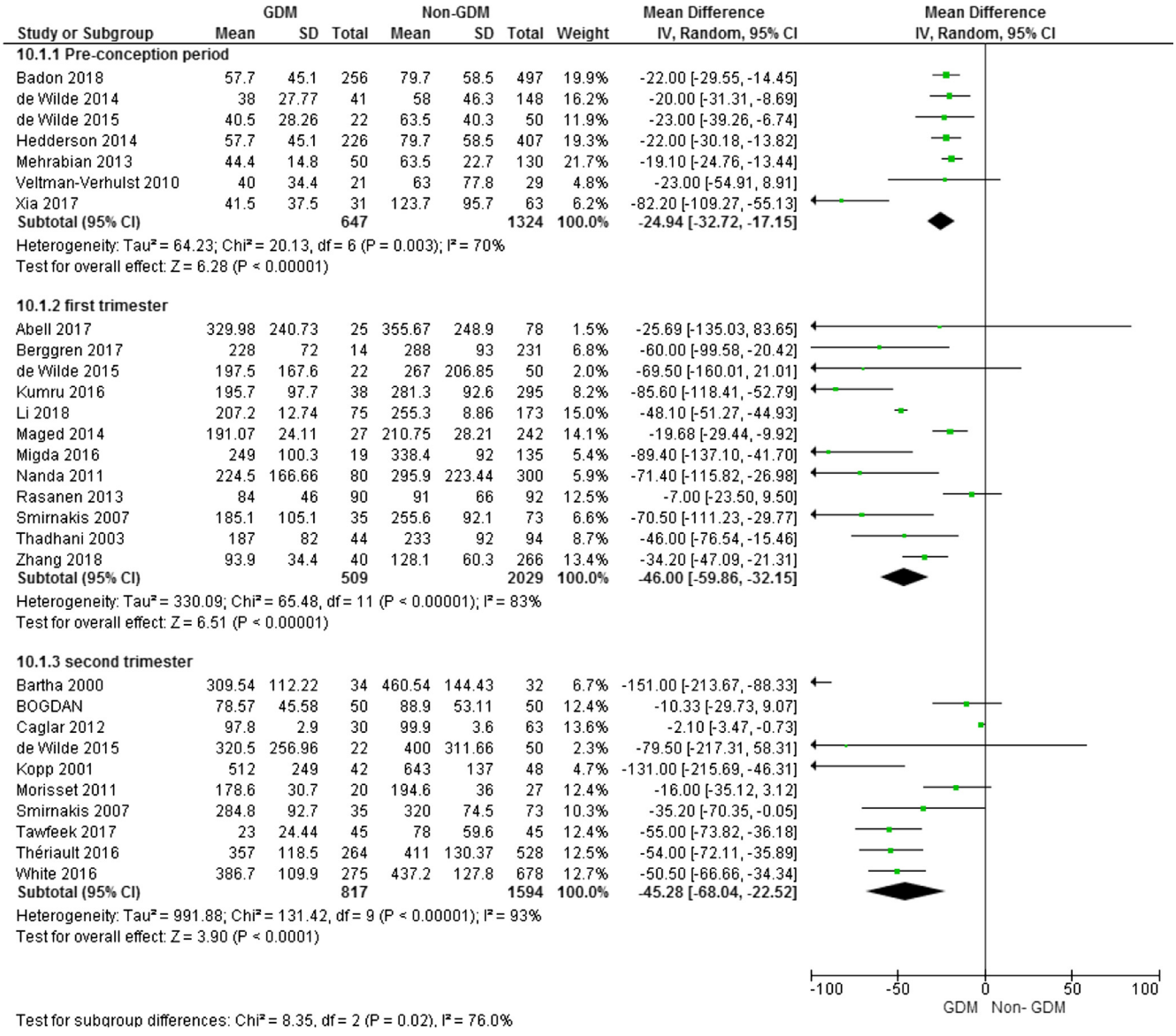


Fig. 9 – Subgroup analysis of serum SHBG level based on different measuring time.

lating the concentration of SHBG. Evidence has shown that there is a strong association between insulin resistance and SHBG as a marker of resistance to insulin [49]. Other factors such genetic factors [50], pre-pregnancy BMI or BMI during pregnancy [36], are also important in variability of SHBG.

In addition, our subgroup analyses of six studies showed a significant decrease of serum SHBG concentration in pregnant women with PCOS and gestational diabetes. The underlying cause may be due to the fact that SHBG binds with testosterone and estradiol and can decrease their biological activities. In PCOS, the production of androgen and estrogen is increased; these increased levels are also caused by a decreased SHBG concentration, due to biologically active circulating levels of estradiol and testosterone. Insulin resistance may reduce the hepatic production of SHBG and significantly increase the production of androgens by the ovaries [51].

Further, our subgroup analysis of nine studies showed a significant decrease in serum SHBG concentration in pregnant obese women with gestational diabetes in comparison to obese women without GDM. It is well known that obesity is strongly associated with inflammation, which in turn may contribute to insulin resistance [52]. Evidence has shown that obesity in pregnancy is associated with a 4–8 times higher risk of developing GDM compared with normal weight during pregnancy [35,36,53]. Evidence revealed that low calorie diet and weight loss could increase the level of SHBG particularly in women [54]. Also the role of exercise in improvement the level of SHBG has been addressed in studies [55].

Our meta-analysis of 26 observational studies provided strong evidence that the serum SHBG level in women with GDM is significantly lower than in the healthy pregnant controls based on different measurement times. The incidence of

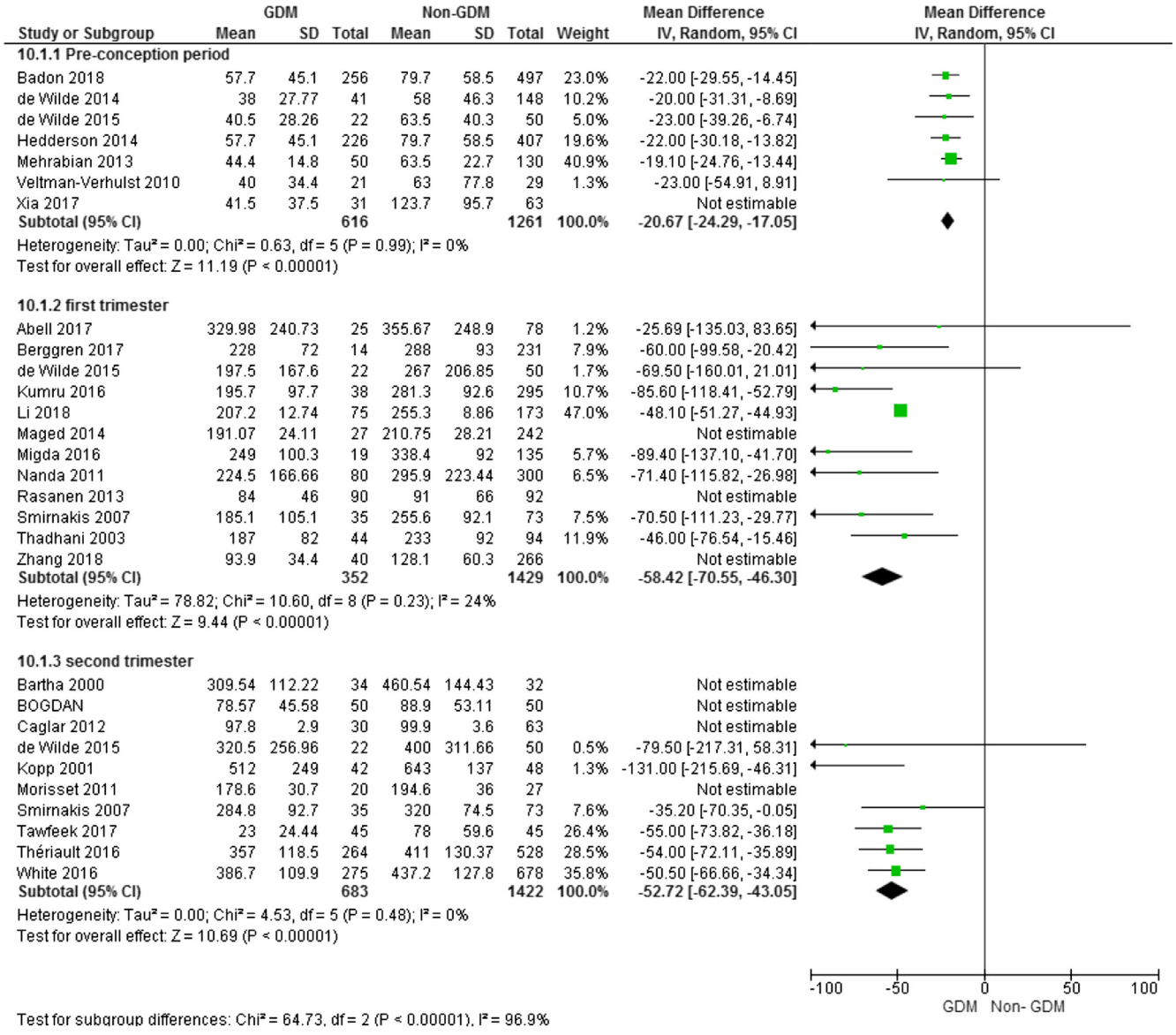
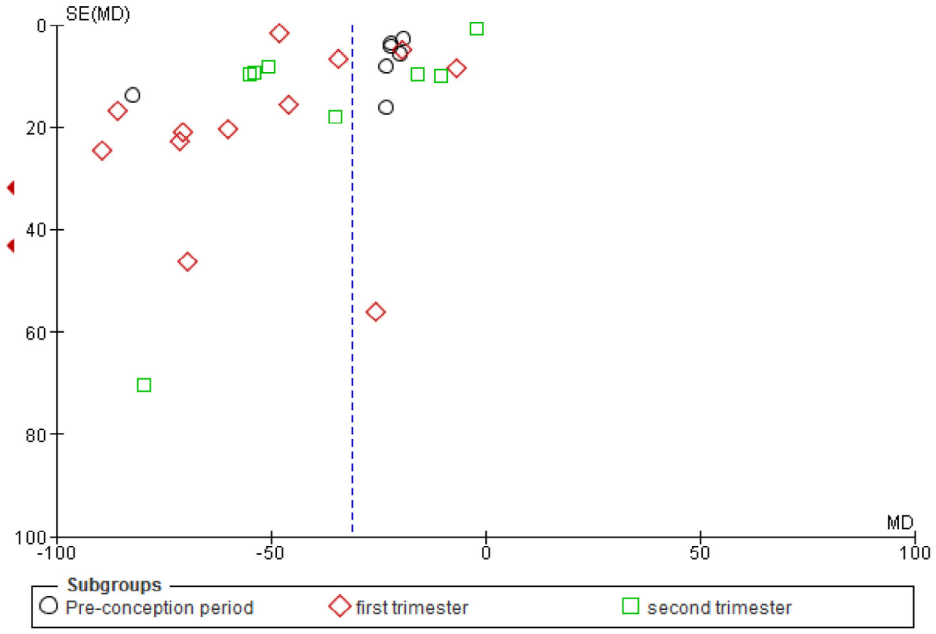


Fig. 10 – Forest plot of sensitivity analysis based on different measuring time of SHBG.

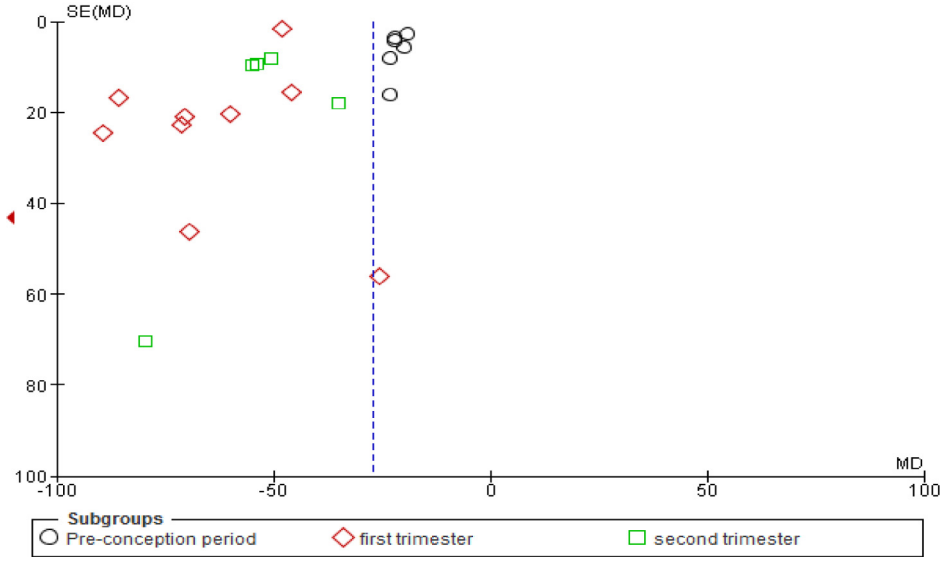
GDM in pregnancy varies between 1 and 14% [56]. Physiological insulin resistance that begins in the second trimester and progresses through the third trimester typically accompanies pregnancy. The etiology and pathogenesis of GDM are complex. Hormones secreted by the placenta lead to an increase in maternal insulin secretion to maintain high blood glucose levels during pregnancy. Exacerbation of pancreatic beta-cell dysfunction or impairment of compensatory increase in insulin secretion from pancreatic cells, or both, results in GDM [57]. This dysfunction can result from either an autoimmune process (a state of chronic insulin resistance) or a genetic abnormality leading to abnormalities of insulin secretion [58].

4.1. *Limitations of study*

There were some limitations for this systematic review. First, publication bias cannot be definitively detected. Second, the measurement methods of SHBG were different among the included studies. Third, different diagnostic criteria of GDM may influence the pooled effect due to the different threshold value for the oral glucose tolerance test. Fourth, some of the studies did not provide enough clinical information, so we could not include them in the meta-analysis. And finally, the high level of heterogeneity was observed in investigating the relationship of SHBG and GDM (I^2 = 97%). After excluding 10 papers the level of heterogeneity was reduced to 46%. The potential causes of this heterogeneity such as; low sample size, fair quality of papers, and different methods for the diagnosis of SHBG may influenced the relationship of GDM and SHBG. Therefore the results of this systematic review for the relationship of GDM and SHBG should be considered with caution. The trim and fill analysis showed that publication bias was existed in this systematic review.



A: Funnel plot of serum SHBG level based on different measuring time



B: Funnel plot of sensitivity analysis of serum SHBG level based on different measurement time

Fig. 11 – A. Funnel plot of serum SHBG level based on different measuring time. B. Funnel plot of sensitivity analysis of serum SHBG level based on different measurement time.

5. Conclusion

This systematic review showed that the level of SHBG is significantly lower in GDM pregnant women than that in healthy women. Therefore, the assessment of this marker in the early stages of pregnancy may be considered as a suggestion. The results of this systematic review about the relationship of GDM and SHBG should be considered with caution. Further studies are required to clarify the role of SHBG in GDM.

6. Availability of data and material

The datasets generated during and/or analyzed during the current study are available from the corresponding author.

7. Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

8. Conflict of interest

There is no any conflict of interest to declare.

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Author contributions

SF, PA, SJ, NJM, ZM, FS, MZ
Study concept and design: SF, PA and SJ
Search: SF, NJM, MZ
Screening: SF, NJM
Data extraction: SF, ZM
Quality assessment: SF, PA, SJ.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.04.028.

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