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Review Article

First-trimester biomarkers for early prediction of gestational diabetes mellitus: a meta-analysis

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Abstract: Gestational diabetes mellitus (GDM) occurs in approximately 7% of all pregnant women. In order to minimize the risk of GDM-associated complications, it is still very important to identify novel biomarkers for early prediction of GDM, particularly in the first trimester. In this study, we conducted a meta-analysis to assess the clinical implications of first-trimester biomarkers, including sex hormone-binding globulin (SHBG), adiponectin and C-reactive protein (CRP), in predicting the risk of GDM. Electronic databases, including Medline, Embase, Scopus, Google Scholar, and Cochrane Library, were searched and fourteen studies including 2479 patients were identified for this meta-analysis. The random-effects model was employed to pool the data from the included studies to determine the difference in the first-trimester serum levels of SHBG, adiponectin, or CRP between patients with GDM and normal pregnancies. Our meta-analysis reveals that GDM patients exhibit significantly lower levels of SHBG (SMD=-0.48; 95% CI=-0.67, -0.28; Z=-4.77, P<0.0001) or adiponectin (SMD=-2.36; 95% CI=-3.39, -1.32; Z=-4.47, P<0.0001) and significantly higher concentrations of CRP (SMD=1.67; 95% CI=0.44, 2.90; Z=2.66, P=0.0079) in the first trimester than those women with normal pregnancies. These findings suggest that SHBG, adiponectin, and CRP may serve as first-trimester biomarkers for predicting the risk of developing GDM in pregnant women.

Keywords: SHBG, adiponectin, CRP, GDM, biomarker

Introduction

Gestational diabetes mellitus (GDM) is a common medical condition characterized by glucose intolerance of varying severity with onset or first diagnosis during pregnancy [1]. GDM has been estimated to occur in ~7% of all pregnancies, resulting in an incidence rate of >200,000 cases every year [2]. If it is not well treated, GDM can lead to a wide range of serious short- and long-term complications, including preeclampsia and type 2 diabetes mellitus for mothers and hyperbilirubinemia and respiratory distress syndrome for fetuses or newborn infants [1].

Screening for glucose intolerance between 24-28 weeks of gestation, using oral glucose tolerance test (OGTT), is the routine procedure that is currently performed to detect GDM, which provides a valuable opportunity to manage those women with GDM [3]. However, this screening procedure during the late second trimester of pregnancy can only allow a brief window for implementing interventions designed to improve the clinical outcomes, particularly for the fetuses [2, 3]. It may take weeks for the diet modification, which is usually the first step to manage GDM patients, to become effective [3, 4]. Additionally, if the diet modifications fail to maintain the blood glucose levels in normal range, medications with insulin or oral glucose-lowering agents, which can be started during the last 4-6 weeks of pregnancy, will be warranted to control blood glucose levels [5]. Therefore, identification of first-trimester biomarkers for early prediction of GDM will provide tremendous benefits to minimize potential harmful effects of GDM on mothers and fetuses/newborn infants.

Interestingly, in recent years, substantial evidence has suggested that certain first-trimester serum markers, including sex hormone-binding globulin (SHBG) [6-11], adiponectin [9, 12-17], and C-reactive protein (CRP) [7, 9, 10, 16, 18, 19], may serve to predict the risk of developing GDM in pregnant women. Specifi-

cally, first-trimester serum levels of SHBG and adiponectin [6-17] have been found to be tremendously lower in pregnant women who later develop GDM, compared with normal pregnancies. Analogously, elevated first-trimester serum levels of CRP are also strongly correlated with the development of GDM [7, 9, 10, 16, 18, 19]. However, these studies have been carried out on a small scale and the results have not been consistent. Thus, it will be necessary to combine the data from those studies to boost statistical power and provide a better estimate of the effect size to evaluate the clinical implications of these first-trimester serum biomarkers in predicting the risk of GDM.

In this study, we performed a systematic review of the literature and carried out a meta-analysis to determine if SHBG, adiponectin and CRP could serve as first-trimester biomarkers for early prediction of GDM. These analyses will provide novel insights into the future clinical implications of these potential biomarkers in the management of GDM patients.

Materials and methods

Literature search

This systematic review and meta-analysis were performed according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [20]. We searched the electronic databases, including the Medline, Embase, Scopus, Google Scholar, and Cochrane Library, to identify potential studies that examined the correlation of first-trimester biomarkers and gestational diabetes mellitus. Search terms, including "SHBG", "Sex hormone-binding globulin", "adiponectin", "C-reactive protein", "CRP", "gestational diabetes mellitus", and "GDM", were used for the literature search. Two investigators (T. Z. and J. Y.) performed the literature search independently.

Study selection

The following criteria were applied to identify eligible studies for this meta-analysis: (1) Serum samples were collected from pregnant women during first trimester to determine the serum levels of SHBG, adiponectin, and CRP, (2) Screening for GDM was performed in all participants between 26 and 30 weeks of gestation with an oral glucose loading test, (3) Studies that determined the effects of first-trimester serum levels of SHBG, adiponectin, or CRP on the development of GDM. All the potentially eligible studies were reviewed and extracted independently by two investigators (T. Z. and J. Y.) and disagreements were resolved by discussion until a consensus was reached.

Data extraction

Abstracts of all relevant studies were reviewed by two investigators (T. Z. and J. Y.). Using a standardized data extraction form, we collected the following data from the retrieved full-text articles: (1) Demographic information, including lead author, publication year, sample size, and mean age, (2) Gestational age at sample collection and OGTT testing, (3) Study design and assays used to determine the serum levels of SHBG, adiponectin, or CRP, (4) First-trimester serum levels of SHBG, adiponectin, or CRP in GDM patients and control subjects.

Definition and standardizations

Determination of pregnancy duration was based on routine ultrasonographic examinations preformed between 10 and 12 weeks of gestations. The definitive diagnosis of GDM was based on the OGTT results. Patients in both case and cohort groups were well-matched at baseline in terms of demographic variables, conventional risk factors, and baseline laboratory values, including SHBG, adiponectin, CRP, glucose, and creatinine. Women with documented glucose intolerance that was diagnosed before pregnancy or at <20 weeks of gestation were considered to have pre-GDM and were excluded from this meta-analysis. All included studies were approved by the Ethical Committee of relevant institutions. All women were provided written informed consent before their inclusion in the study.

Statistical analysis

All statistical analyses were carried out using the statistical software R (version 3.0.2, R Foundation for Statistical Computing, Vienna, Austria) and the package "meta" (Developed by Dr. Guido Schwarzer, Institute for Medical Biometry and Statistics, Freiburg, Germany) was used to pool the data from the eligible studies for statistical analysis. The random-effects model based on the inverse variance method was em-

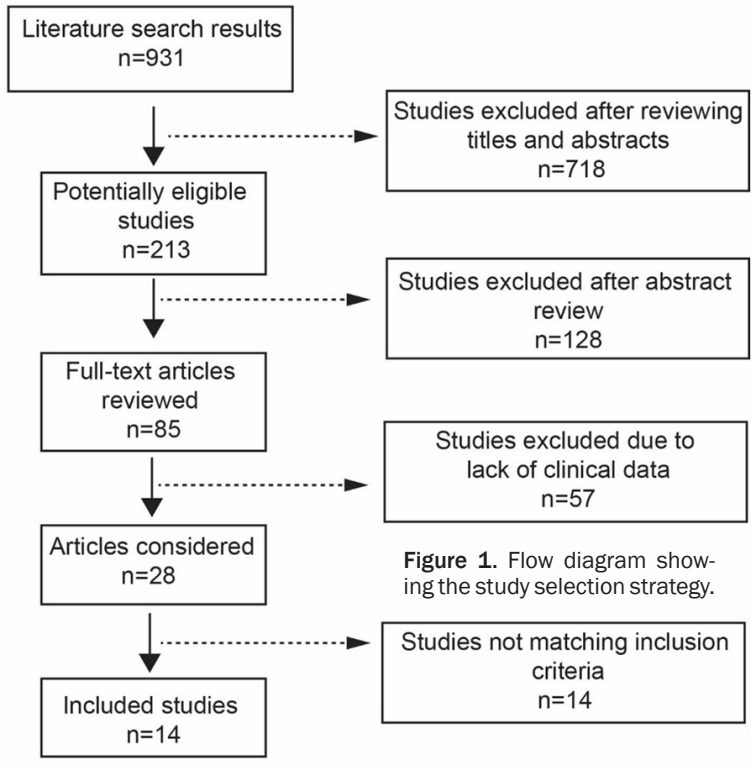

Figure 1. Flow diagram showing the study selection strategy.

ployed to calculate the standardized mean difference (SMD) and 95% confidence interval (CI) in an effort to determine the difference in the first-trimester serum levels of SHBG, adiponectin, or CRP between patients with GDM and normal pregnancies. The statistical heterogeneity among different studies was quantitated by the Tau^2 and I^2 statistics [21]. If *P* value was less than 0.1, heterogeneity was considered significant. The degree of heterogeneity was also determined by the I^2 (0-40%: low heterogeneity; 30-60%: moderate heterogeneity; 50-90%: substantial heterogeneity; 75-100% considerable heterogeneity) [21, 22]. In order to evaluate the robustness of the findings from our meta-analyses, we carried out sensitivity analyses to compare the differences in pooled estimates before and after certain included studies were removed from our meta-analyses.

Results

Characteristics of eligible studies

We initially identified 931 relevant studies using the search strategies as described above. After thoroughly reviewing the titles and abstracts of those reports, 718 articles were excluded from further screening because of lack of desirable clinical data, including first-trimester serum levels of SHBG, adiponectin, and CRP (**Figure 1**). Eventually, fourteen studies including 2479 patients were identified to meet the criteria for this meta-analysis (**Figure 1**) [6-19]. Of those reports, the correlation of first-trimester serum levels of SHBG or adiponectin with the risk of GDM was determined in six [6-11] or seven studies [9, 12-17], respectively, while another six studies examined the association of first-trimester CRP levels with the risk of GDM [7, 9, 10, 16, 18, 19] (**Table 1**).

Notably, all reports that are included in this meta-analysis employed a study design of prospective cohort studies, including nested case-control, cross-sectional, and cohort studies to determine the relationship between the biomarkers (SHBG, adiponectin, and CRP) and the risk of GDM (**Table 1**). The levels of SHBG, CRP and adiponectin were measured using either ELISA or RIA kits from serum samples that had been collected in the first trimester except that in one study SHBG levels were determined from the serum samples collected at 13-16 weeks of pregnancy (**Table 1**). The definitive diagnosis of GDM was made at 23-30 weeks of pregnancy based on OGTT testing (**Table 1**).

The methodologic quality of each included study was assessed according to the GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) guidelines [23, 24]. The overall quality of each study can be rated as high, intermediate, moderate, low, or very low quality, when the following elements are taken into consideration: study design, study quality, the consistency of results across studies, the directness of the evidence, and study precision [23, 24]. Based on these grading guidelines, twelve studies of the included reports [6, 7, 9-16, 18, 19] are classified as high quality, whereas two studies [8, 17] are graded as intermediate quality (**Table 1**).

Table 1. Characteristics of included studies

Studies	Pt No.	Mean age (years)	Country	Markers	Detection methods	Gestational age at sample collection (weeks)	Gestational age at OGTT (weeks)	Study design	Quality of included studies
Berggren (2014)	51	28.7	USA	CRP	ELISA	<14	24-28	Cross-section	High
Caglar (2012)	93	28.9	Turkey	SHBG	RIA	13-16	24-28	Cross-section	High
Chen (2006)	172	24.8	USA	CRP	ELISA	15	28	Nested Case-control	High
Georgiou (2008)	28	33.2	Australia	Adiponectin	ELISA	11.3	28	Nested Case-control	High
Ianniello (2013)	32	31.8	Italy	Adiponectin	ELISA	8-11	23-25	Cohort	High
Lacroix (2013)	483	28.4	Canada	Adiponectin	RIA	6-13	24-28	Cohort	High
Lain (2008)	59	28.2	USA	Adiponectin	RIA	9.3	24-28	Nested Case-control	High
Liu (2011)	48	25-35	China	CRP, Adiponectin	ELISA	9-12	24-28	Nested Case-control	High
Low (2010)	79	N/A	Malaysia	Adiponectin	ELISA	<18	N/A	Cross-sectional	Immediate
Maged (2013)	269	27.0	Egypt	SHBG, CRP	ELISA	11.19	26.23	Nested Case-control	High
Pan (2007)	775	29.9	China	SHBG	ELISA	9.62	24-28	Nested Case-control	Immediate
Rasanen (2013)	182	28.8	USA	SHBG, CRP, Adiponectin	ELISA	9.9	24.1	Nested Case-control	High
Smirnakis (2007)	108	32.2	USA	SHBG, CRP	ELISA	11	27.8	Nested Case-control	High
Thadhani (2003)	138	32.5	USA	SHBG	ELISA	10.3	26-30	Nested Case-control	High

ELISA, enzyme-linked immunosorbent assay; RIA, Radioimmunoassay; Pt. No, patient number; OGTT, oral glucose tolerance test.

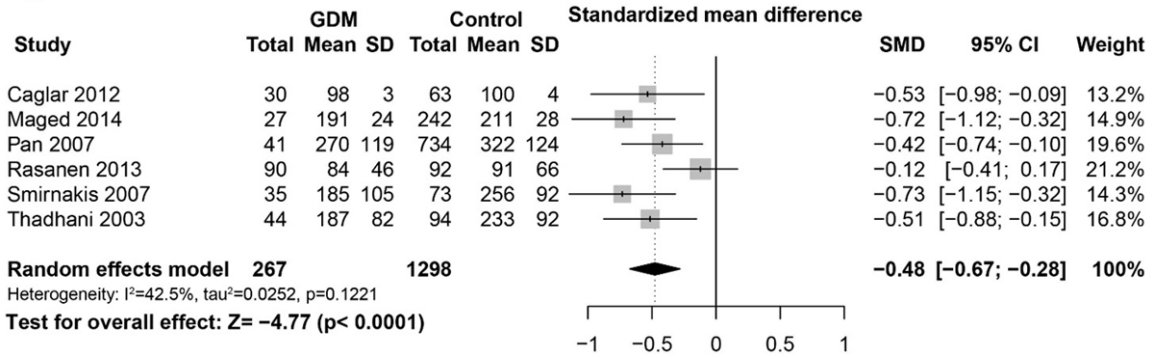

Figure 2. First-trimester serum levels of SHBG are significantly lower in GDM patients compared with women with normal pregnancies. Seven studies were identified as described in the Methods section. SMD and 95% CI were calculated using the inverse variance statistical method based on the random-effects model. Additionally, the degree of heterogeneity among different studies was determined with the Tau^2 and I^2 statistic. The square boxes represent individual effect of the included studies. The sizes of the square boxes are proportional to the samples sizes of the corresponding studies, whereas the length of the horizontal lines through the square boxes represents the 95% CI. The overall estimate and its 95% CI are shown as a black diamond with its center denoting the pooled point estimate and its horizontal tips indicating the 95% CI.

First-trimester SHBG levels are negatively associated with the development of GDM

SHBG is a glycoprotein produced by the liver and its secretion is negatively regulated by insulin [25, 26]. Furthermore, decreased levels of SHBG have been found to be associated with insulin resistance and the development of type 2 diabetes [25, 26]. Therefore, we first conducted a meta-analysis of six eligible studies [6-11] to determine if first-trimester SHBG levels are associated with the risk of GDM. Intriguingly, as illustrated in the forest plot (**Figure 2**), our meta-analysis shows that pregnant women who develop GDM exhibit significant lower levels of SHBG in the first trimester than normal control subjects (SMD=-0.48; 95% CI=-0.67, -0.28; Z=-4.77, P<0.0001), indicating that lower concentrations of SHBG in pregnant women are predictive of the development of GDM.

First-trimester adiponectin levels are inversely correlated with the risk of GDM

Adiponectin, a protein hormone secreted by adipose tissues and the placenta in pregnancy, is involved in regulating glucose levels as well as fatty acid breakdown [27]. Moreover, hypoa-

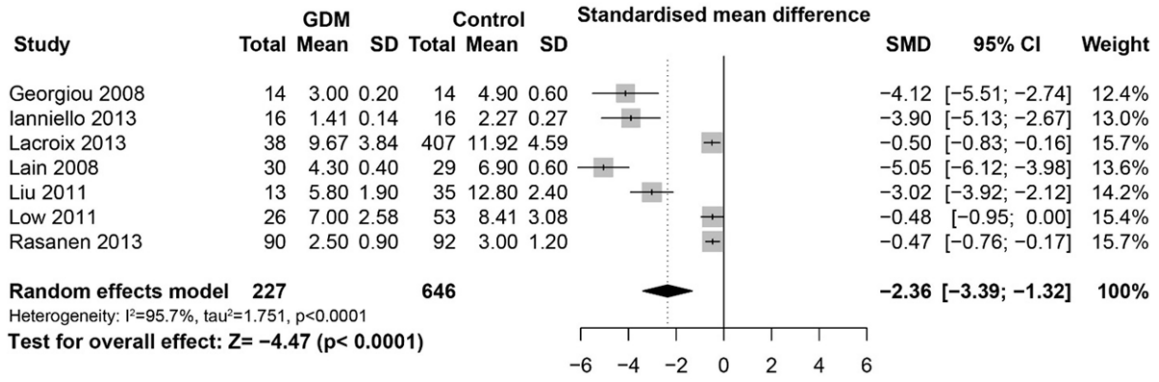

Figure 3. First-trimester serum levels of adiponectin are significantly lower in GDM patients compared with women with normal pregnancies. SMD and 95% CI were calculated from the seven studies using the same methods as described in **Figure 2**.

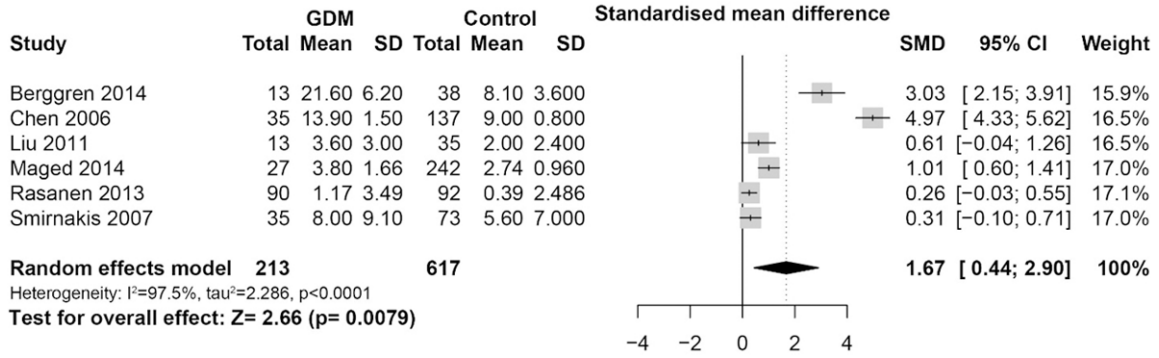

Figure 4. GDM patients exhibit significantly higher serum levels of first-trimester CRP, compared with women with normal pregnancies. SMD and 95% CI were obtained from the six studies using the same methods as described in **Figure 2**.

diponectinemia has also been implicated in insulin resistance and type 2 diabetes [28]. To examine the correlation of first-trimester adiponectin levels with the risk of developing GDM, we then performed a meta-analysis of the seven studies [9, 12-17] that compared the incidence of GDM in pregnant women with low and high levels of first-trimester adiponectin. We find that first-trimester adiponectin levels are significantly reduced in pregnant women who develop GDM than those in normal pregnancies (SMD=-2.36; 95% CI=-3.39, -1.32; Z=-4.47, P<0.0001) (**Figure 3**), suggesting that decreased concentrations of adiponectin in pregnant women also predict the risk of developing GDM.

Elevated first-trimester CRP levels predicts increased risk of developing GDM

As an inflammation marker, elevated levels of CRP have also been found to be correlated with an increased risk of developing type 2 diabetes mellitus [29]. We then pooled the data from six eligible studies [7, 9, 10, 16, 18, 19] to examine the relationship between first-trimester CRP levels and the risk of GDM. Interestingly, the pooled data from our meta-analysis of the six studies demonstrate that pregnant women who develop GDM display significant higher serum levels of CRP in the first trimester than normal control subjects (SMD=1.67; 95% CI=0.44, 2.90; Z=2.66, P=0.0079) (**Figure 4**). These data show that increased concentrations of first-trimester CRP also correlate with the risk of developing GDM in pregnant women.

Sensitivity analysis

Next we performed sensitivity analyses to test the robustness of the results from our meta-analyses. Exclusion of the study [6] in which RIA was used to measure SHBG levels from the meta-analysis does not dramatically affect the

Table 2. Sensitivity analysis

Biomarkers analyzed	Pooled estimates before exclusion analysis	Pooled estimates after exclusion analysis
SHBG	SMD: -0.48	SMD: -0.47
	95% CI: (-0.67, -0.28)	95% CI: (-0.70, -0.24)
	Z=-4.77	Z=-4.03
	P<0.0001	P<0.0001
Adiponectin	SMD: -2.36	SMD: -2.26
	95% CI: (-3.39, -1.32)	95% CI: (-3.54, -0.99)
	Z=-4.47	Z=-3.48
	P<0.0001	P=0.0005
CRP	SMD: 1.67	SMD: 0.95
	95% CI: (0.44, 2.90)	95% CI: (0.29, 1.61)
	Z=2.66	Z=2.83
	P<0.0079	P=0.0047

SHBG, sex hormone-binding globulin; CRP, C-reactive protein; SMD, standardized mean difference; CI, confidence interval.

overall effect (SMD=-0.468; 95% CI=-0.67, -0.267; Z=-4.55; P<0.0001) (**Table 2**). Similarly, first-trimester adiponectin levels are still significantly lower in GDM patients compared with women with normal pregnancies (SMD=-2.26; 95% CI=-3.54, -0.99; Z=-3.48; P=0.0005), when two studies [14, 15] in which RIA was employed to determine adiponectin levels were excluded from the meta-analysis (**Table 2**). Additionally, removal of the outlier study [19] does not affect the clinical significance of increased first-trimester CRP levels as a potential biomarker to predict the risk of GDM (SMD: 0.95; 95% CI: 0.29 to 1.61; Z=2.83; P=0.0047) (**Table 2**). These sensitivity analyses indicate that the findings of our study are robust and uncertainty involving this meta-analysis is very minimal.

Discussion

GDM is an increasingly common medical disorder during pregnancy with well-documented maternal and fetal complications, ranging from preeclampsia for the mother to macrosomia and hypoglycemia for the fetus [1, 2]. Identification of reliable first-trimester biomarkers for predicting the risk of developing GDM would offer invaluable opportunities to better manage patients with GDM and markedly reduce adverse pregnancy outcomes. In this study, our meta-analyses of the fourteen studies including 2479 patients show that pregnant women who develop GDM during pregnancy display significantly lower levels of SHBR or adiponectin and significantly higher concentrations of CRP during the first trimester than those in normal pregnancies. These findings suggest that first-trimester serum levels of SHBG, adiponectin or CRP may serve to predict the risk of developing GDM in pregnant women.

Insulin resistance, which is defined as a condition that requires more insulin to maintain glucose homeostasis compared with a normal state, increases throughout pregnancy [30] and is one of the key features of GDM [31]. Insulin resistance can result from any defects in the insulin signaling cascades, including the activation of insulin receptor tyrosine kinase, phosphorylation of the insulin receptor substrate (IRS) proteins and downstream phosphoinositide-3-kinase (PI3K)/Akt signaling pathway [32]. Recent studies indicate that adiponectin or CRP regulates insulin sensitivity through modulating one component of the signaling pathways [33, 34]. For example, adiponectin enhances insulin sensitivity by increasing IRS-2 expression in the liver cells of a mouse model [33]. Likewise, CRP has been reported to inhibit insulin-induced IRS tyrosine phosphorylation and PI3-K/Akt activation in a rat model [34]. The mechanism by which low SHBG levels reduce insulin sensitivity is still not well documented. SHBG may directly bind to its cellular receptors such as G protein-coupled receptors on the plasma membrane, independent of its binding to androgen in the circulation, and activate adenylyl cyclase, resulting in production of cyclic adenosine monophosphate and subsequent increased glucose uptake and improved insulin sensitivity [35, 36].

In this study, we, for the first time, employed a systemic review and meta-analysis approach to investigate the clinical significance of SHBG, adiponectin and CRP as first-trimester biomarkers to predict the risk of developing GDM in pregnant women. However, it is worth noting that the number of reports that was eligible and included in our study is relatively small. Hence, we did not assess publication bias regarding our meta-analyses [21, 37]. Additionally, the patient numbers from the eligible studies are not very large. Furthermore, different experimental approaches (either RIA or ELISA) or RIA/

ELISA kits from different companies were utilized to determine the serum levels of SHBG, adiponectin or CRP in the included studies. These inconsistencies may lead to significant between-study variations as we observed above. Thus, further cohort studies with larger sample sizes using a consistent experimental condition to measure the serum levels of SHBG, adiponectin or CRP are warranted to validate the findings we presented here in the future.

Taken together, our meta-analysis suggests that first-trimester serum levels of SHBG, adiponectin and CRP can be employed to predict the risk of developing GDM in pregnant women. These findings provide novel insights into the management of patients with GDM in the future.

Disclosure of conflict of interest

None.

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