First Trimester Potential Biochemical Predictive Tests for Gestational Diabetes Mellitus: A Systematic Review

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Abstract

Objective: Gestational diabetes mellitus (GDM) is the most common metabolic complication during pregnancy. So, a large number of studies have evaluated the usefulness of different screening tests. The aim of this study was focused on the potential of only first-trimester screening used in the prediction of GDM.

Materials and Methods: In this systematic review, we searched PubMed, EMBASE, and Scopus (between 2010 and 2020) and also searched the reference lists of the relevant articles manually. After performing a thorough evaluation of the 242 potentially eligible papers, only 60 papers were selected in terms of the inclusion criteria. Search key terms were combining 'Gestational diabetes' or 'GD' "gestational diabetes mellitus" or" GDM" or pregnancy-induced diabetes' with at least one of the following terms: "screening test", "first-trimester", "prediction", "marker predictor", "serum marker".

Results: A total of 161954 pregnant women were evaluated in these reviewed studies. Moreover, many tests were assessed in the first trimester of pregnancy to predict GDM. This review showed that hs-CRP, FPG, TG, and LDL-C along with maternal BMI in the first trimester were related to the increased risk of developing GDM. Other tests were used in only one or two studies.

Conclusion: This review showed that hs-CRP, FPG, TG, and LDL-C along with maternal BMI in the first trimester were linked to an increased risk of developing GDM. It is recommended that further well-designed studies by considering the cost-effective advantages of these predictive tests, should be performed.

Keywords: Gestational diabetes, First trimester, Biomarker, Review

Introduction

Gestational diabetes mellitus (GDM) is outlined as glucose intolerance, which is 1st detected throughout gestation (1). Accordingly, it is also the most common metabolic complication in pregnant women (2). The prevalence rate of GDM increases over the past decade appears to rise with obesity and type 2 diabetes rates worldwide (3). The prevalence of GDM has been progressively increasing, especially in

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developing countries (4). Also, 75 g oral glucose tolerance test (OGTT) for GDM diagnosis is usually performed between 24-28 weeks' gestation. However, there is still no consensus in the international community on the best method of screening and diagnosis of GDM (5). Moreover, diagnosing GDM at the end of the second trimester of pregnancy has been questioned, due to the possible postponement in achieving the positive effects of pharmacological therapy, diet, and exercise on placental vascularity, fetal development, and mother morbidity (6). However, evidence indicated that pregnant women with GDM may show metabolic alterations, at the early stages of pregnancy (7). Measurement of the first trimester biomarkers may identify the patients who are at risk for GDM during early gestation and may allow more time for interventions that can improve the GDM pathogenesis. Recently, some studies have examined the role of biochemical in gestational diabetes, and the results have been reported to be contradictory (5,8-12).

The quest for effective screening scales for the early diagnosis of GDM has intensified within the last few years. Many of the studies have been concentrated on the individual protein markers of insulin resistance and inflammation, and also on investigating the combining biochemical markers with pregnancy risk factors such as sex hormone-binding globulin (SHBG), high sensitivity C-reactive protein (hs- CRP), homeostasis model assessment (HOMA) protein-5, insulin growth factor, insulin sensitivity, tissue plasminogen activator [t-PA], zonulin, and C-reactive protein (CRP) (13-16). Reviews of these studies would facilitate the appropriate decisions by summarizing the existing knowledge. In this regard, this study was focused on the potential of only first-trimester screening used in the prediction of GDM. The obtained results allow for early detection and timely interventions, which will hopefully improve maternal and fetal outcomes in the future.

Materials and Methods

Search strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria (17). were followed in this study (Tables 1 and 2). A systematic literature search of eligible studies was conducted using PubMed, EMBASE, and Scopus databases from January 2010 to March 2020 studies evaluating the association between first trimester or early pregnancy prenatal screening biomarkers levels and GDM development. Search key terms were formed in the abstracts and titles and keywords by combining ‘Gestational diabetes’ or ‘GD’ “gestational diabetes mellitus” or” GDM” or pregnancy-induced diabetes’ with at least one of the following terms: “screening test”, “first-trimester”, “prediction”, “marker predictor”, and “serum marker” using the operator “AND”. To maximize the coverage of our literature no filters or limits were placed on the searches. But the language was restricted to English, Persian, and Turkish articles.

Inclusion and exclusion criteria

Articles were eligible for inclusion in this systematic reviews if they meet the following criteria: 1) an original, published, observational study that examined the association between first-trimester screening biomarker and diagnosis of GDM; 2) included a comparison group of women who didn't develop GDM (i.e., normoglycemic pregnancies). Review articles, editorials, and non-human studies (i.e., cell culture or animal studies) and case reports or short communication, and non-full text articles were excluded. Articles were additionally excluded if GDM was combined with impaired glucose tolerance.

Study selection

Two authors independently evaluated the 242 search results in terms of eligibility and resolved cases of disagreement through consensus. After initial assessments, 131 irrelevant, duplicate, review, and guideline

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studies were excluded. The abstracts and titles of the remaining 111 articles were then reviewed and 37 more studies were excluded. In the next stage, the full texts 62 remaining articles were evaluated and 13 articles that did not match the aim and/or inclusion criteria of this study were excluded. 12 included articles were searched for the reference lists of all relevant articles. Finally, 60 eligible articles were reviewed (Figure 1).

Quality assessment

The quality of the quantitative studies was applied using an adaptation of the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist. The STROBE checklist included 22-item with the following domains: eligibility criteria, method of variable assessment, participant characteristics, reporting of summary measures outcome events, and discussion of sources of bias and/or imprecision.

Data extraction

Data was extracted from full-text articles by two independent authors. Disagreements were resolved by consulting a third author until a consensus was reached. The selected papers were thoroughly evaluated and the required data: Author (year), country, publication date, weeks of gestation at the time of assessment, the screening tests, time of diagnosis, STROBE score, and test results were recorded.

Results

After the removal of repetitive, titles, and abstracts, the remaining citations were thoroughly applied for potential inclusion based on our inclusion criteria (Figure 1). Accordingly, a total of 60 studies were eligible in terms of the inclusion criteria. Studies have been conducted on various factors for the early

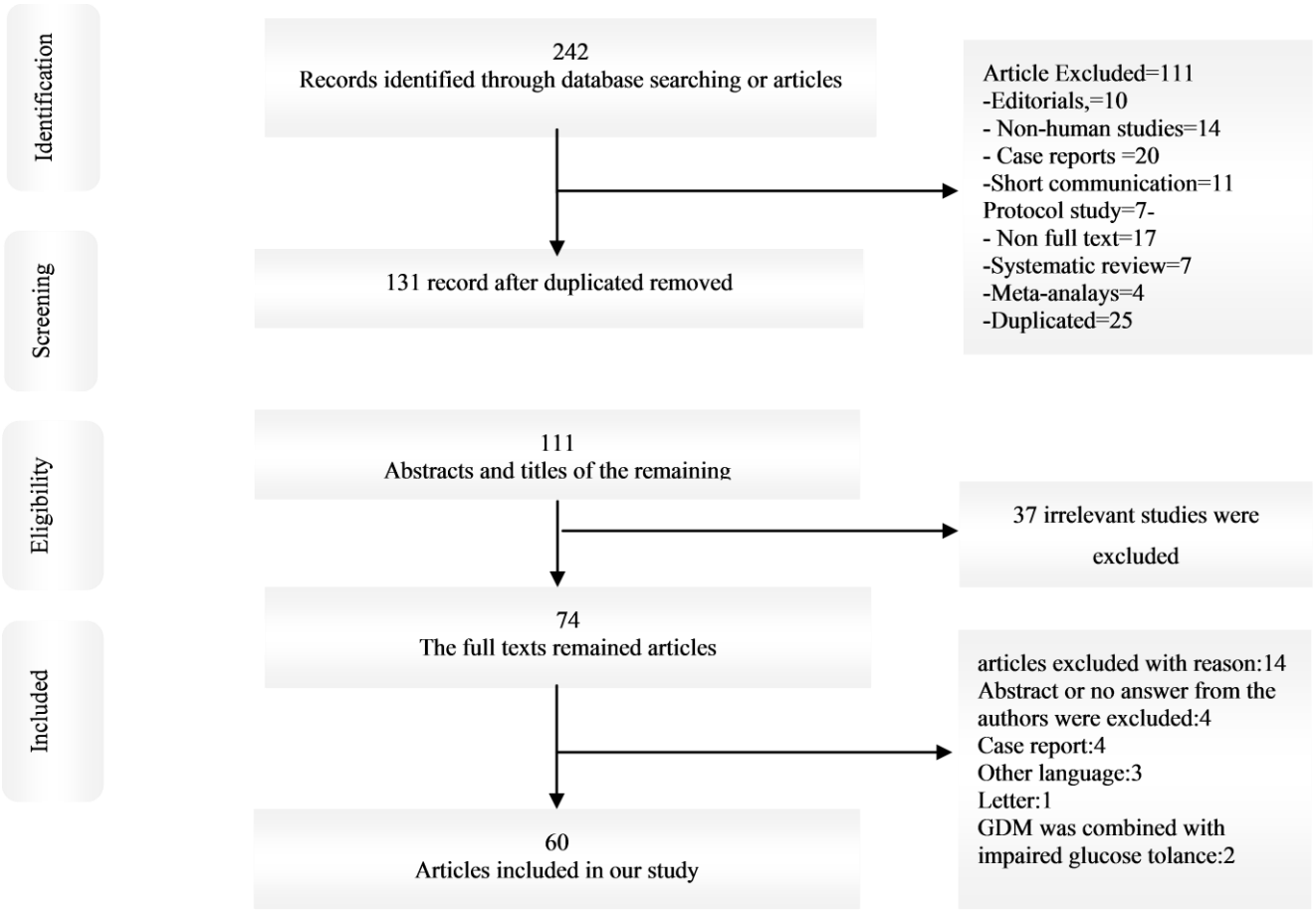


Figure 1. Flowchart of article selection

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diagnosis of GDM. Table 1 presents a brief description of the selected studies and their findings.

Table 1. Characteristics of studies included in the review of first-trimester prenatal screening biomarker levels and GDM development, January 2010-March 2020.

Author(year)	Country	Strobe score	Weeks of Gestation when measured	Applied Screening tests	Time of diagnosis	Results	Risk of bias Reported by authors
Dereke J, et al (2020)	Sweden	22	13.6 ± 2.8 week	PAPP-A2	28 week	Increased PAPP-A2 was associated with gestational diabetes *P*-value< 0.001	NR
Kapustin RV, et al (2020)	Russia	22	110 to 13+6 week	PAPP-A, free B hCG	28 week	PAPP-A and free B-hCG tests cannot be used as a tool of risk identification GDM	NR
Visconti F, et al (2019)	Italy	22	11–13 weeks	combined test (FTCT) (NT, PAPP-A, free B hCG)	24–28 weeks	FTCT is positively and significantly associated with GDM risk. B-hCG >2.0 MoM had a reduced risk of GDM. PAPP-A <1 was associated with GDM	NR
Caliskan R, et al (2020)	Turkey	20	11–13 weeks	PAPP-A, free B hCG	24–28 weeks	Serum PAPP-A was significantly lower when compared with the Control Groups. There was either no significant differences regarding free β -hCG concentrations among the groups	NR
Sirikunalai P, et al (2016)	Thailand	20	11–13 weeks	free B hCG	24–28 weeks	High free β -hCG levels may decrease the risk of GDM.	NR
Savvidou MD , et al (2016)	UK	20	11+0–13+6 weeks	free b-hCG - PAPP-A	24–28 weeks	There was no significant difference between the groups in maternal free B-hCG MoM. Maternal PAPP-A, was significantly lowered in diabetes, compared with the non-diabetic group	
Husslein H, et al (2012)	Austria	20	11 - 14 week	PAPP-A - free β - hCG	24–28 weeks	PAPP-A and β -hCG were not significantly associated with GDM risk	Diagnosis was not divided between pregestational and GDM"
Lovati E, et al (2013)	Italy	19	first trimester	PAPP-A	24–28 weeks	Low PAPP-A was strongly associated with GDM	NR
Beneventi F, et al(2011)	Italy	19	First trimester	PAPP-A	24–28 weeks	PAPP-A concentrations were lower among case group than in the control group	NR
Beneventi F, et al (2011)	Italy	20	first trimester	PAPP-A- sHLA-G).	24–28 weeks	Lower PAPP-A and sHLA-G are independent markers of GDM.	NR
Kulaksizoglu S, et al(2013)	Turkey	20	11 - 14 weeks	PAPP-A- free B hCG	24-28 weeks	Women who developed GDM had significantly lower PAPP-A. But there was no significant difference between the groups in maternal free B-hCG MoM.	NR
Naser W, et al (2019)	Sudan	22	11 - 14 week	hs-CRP- magnesium	24-28 weeks	hs-CRP and serum magnesium levels were not correlated with GDM	NR
Zheng T, et al (2019)	Chinese	22	from 8 to 20	FPG- TG	24-26 weeks	FPG and TG predicted GDM	NR
Kansu-Celik H, et al (2019)	Turkey	21	11–14 week	fetuin-A and hs-CRP- FPG	24-28 weeks	Reduced fetuin-A, elevated hs-CRP, and FPG levels can be used for the early detection of GDM	NR

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Author (year)	Country	Strobe score	Weeks of gestation when measured	Applied screening tests	Time of diagnosis	Results	Risk of bias Reported by authors
Arbib N, et al (2019)	Israel,	20	first trimester	HbA1C	24-28 weeks	Higher HbA1C was associated with gestational diabetes.	the study was biased towards a high-risk population of women that for unknown reason were referred for HbA1C measurement
Correa PJ, et al (2019)	Santiago de Chile,	22	first trimester	Cholestero-triglycerides Insulin growth factor - t-PA- SHBG-ALT-AST-LDL-HDL-leptin and PGF-HOMA	24-28 weeks	Cholesterol (*P*-value=0.04), triglycerides (*P*-value=0.003), insulin (*P*-value=0.003), t-PA (*P*-value=0.0088) and HOMA (*P*-value=0.003) and an increased mean concentration of LDL (*P*-value=0.009) when compared to the control group	NR
Lekva T, et al (2018)	Scandinavian	21	14–16 weeks	75 g OGTT	30–32 weeks	Was not suitable as a screening test to diagnose the women who are likely GDM	NR
Zhang T, et al (2018)	China	19	first trimester	SHBG	24-28 weeks	Decreased SHBG concentrations predict GDM development	NR
Inan C, et al (2018)	Trakya University	20	110/7 -136/7 weeks	PAPP-A-PROK1	24-28 weeks	Lower PROK1 levels are associated with the development GDM	NR
Nevalainen J, et al (2016)	Finland.	20	First-Trimester	Arginine, glycine, 3-hydroxy isovalerylcarnitine ,	24-28 weeks	Arginine, glycine, and 3-hydroxy-isovalerylcarnitine, were significant differences between controls and GDM	NR
Ohara R, et al (2016)	Japan	20	first trimester	hyperemesis gravidarum	24-28 weeks	Positive GDM screening test was significantly higher in the case group compared in the control group	NR
Amylidi S , et al (2016)	Switzerland	19	First-trimester	HbA1c	24-28 weeks	Higher HbA1c levels and values ≥6.0% were predicted of GDM.	NR
Ozgu-Erdinc AS, et al (2015)	Turkey	20	11 - 14.week	FPG -FPI-hs-CRP	24-28 weeks	FPG and hs-CRP were correlated with later development of GDM	NR
Gözükara YM, et al (2015)	Turkey	21	11–14 weeks	Total testosterone	24-28 weeks	Total testosterone has a low testing power for GDM screening and cannot be used as a marker alone.	NR
Rasanen JP, et al (2013)	Pennsylvania	20	5–13 weeks	Fibronectin, adiponectin, SHBG, placental lactogen, and hCRP	22.2 ± 6.2 weeks	Glycosylated fibronectin is a potential biomarker for the early identification of women at risk for GDM.	Potential source of bias is the variation in time between sample collection and administration of the OGTT in GDM case group s
Hamid AM, et al (2015)	Iran	19	11-13 weeks.	Hemoglobin levels	24-28 weeks	Higher hemoglobin levels were at an increased risk of developing gestational diabetes	NR

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Author (year)	Country	Strobe score	Weeks of gestation when measured	Applied screening tests	Time of diagnosis	Results	Risk of bias Reported by authors
Caglar GS, et al (2012)	Turkey	19	13 and 16 weeks'	SHBG	24-28 weeks	SHBG is valuable for screening of GDM	NR
Grewal E, et al (2012)	India	22	Before 12 weeks.	Insulin sensitivity	24-28 weeks	Hyperinsulinemia predicted the development of GDM	NR
Plasencia W, et al (2011)	UK	21	6–14 weeks'	Glucose Challenge Test (GCT) and GTT	20-30 week	Effective diagnosis of GDM is achieved by lowering the GCT and GTT plasma glucose cutoffs.	NR
Nanda S, et al (2011)	UK	18	11 to 13 weeks'	Adiponectin, follistatin-like-3 (FSTL3)-SHBG	24-28 weeks	Adiponectin and SHBG was lower ($p < 0.05$), but FSTL3 was not significantly different.	NR
Savvidou M, et al (2010)	UK	21	first-trimester	t-PA-lipids, hCRP	24-28 weeks	Increased t-PA and low HDL cholesterol levels were significant predictors of GDM	Many control subjects did not have an OGTT
Falcone V , et al (2019)	Vienna	20	12 to 13 week	FPG, fasting insulin(FI), fasting C-peptide (FCP), and HbA1c.	24-28 weeks	Elevated fasting levels of FPG and FCP were associated with an increased risk of developing GDM	NR
Bawah AT, et al (2019)	India	20	first trimester	zonulin and lipids	24-28 weeks	Elevated zonulin was a good predictor of GDM.	NR
Ravnsborg T, et al (2019)	Denmark	22	first trimester	Three proteins; afamin, serum amyloid P-component - vitronectin	11-14 week	Elevated afamin, serum amyloid P-component, and vitronectin were confirmed as predictors of GDM	The use of immuno-affinity depletion of the most abundant serum proteins is a known source of bias.
Kansu-Celik H, et al (2019)	Turkey	21	first trimester	HbA1c and FPG	24-28 weeks	HbA1c and FPG combined enhanced the predictive capability for GDM.	NR
Li J, et al (2018)	Chinese	22	first trimester	Glycoursodeoxycholic acid (GUDCA)-deoxycholic acid (DCA)	24-28 weeks	Serum GUDCA $\leq$ 0.07 nmol/mL and DCA $\leq$ 0.28 nmol/mL were independently associated with a higher risk of GDM	Unadjusted bias was minimal.
Wang P, et al (2018)	China	21	first trimester	FPG and irisin	24-28 weeks	Low plasma levels of irisin were associated with the increased risk of GDM	There was a bias. Women with GDM have higher levels of insulin.
Corcoran SM, et al (2018)	Ireland	22	first trimester	C-reactive protein, SHBG, adiponectin and 1,5 anhydroglucitol	24-28 weeks	Adiponectin and 1,5 Anhydroglucitol were potential biomarkers for predict of GDM.	NR
Bozkurt L, et al (2018)	Italy	22	first trimester	Leptin and adiponectin	24-28 weeks	Adiponectin and leptin were significant differences between GDM women and controls	NR
Benaiges D, et al (2017)	Spain	22	first trimester	HbA1c	24-28 weeks	HbA1c did not have sufficient sensitivity or specificity to diagnose GDM,	Who chose to continue follow-up from other centers; this could act as a potential election bias to gather data

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Author (year)	Country	Strobe Score	Weeks of Gestation when Measured	Applied Screening Tests	Time of diagnosis	Results	Risk of bias Reported by authors
Wang C, et al (2017)	China.	22	first trimester	Total cholesterol (TC), TG, HDL-C, and LDL-C	24-28 weeks	High levels of TC, TG, LDL-C, and low level of HDL-C predicted GDM	Due to the large number of participants excluded, there was the risk of selection bias.
Tu W-J, et al (2017)	China.	21	first trimester	Fatty acid-binding protein 4	24-28 weeks	High fatty acid-binding protein 4 were associated with an increased risk of GDM	NR
Hao M, et al (2017)	China	20	first trimester	FPG	24-28 weeks	High FPG predict later GDM risk	Included its retrospective design and unavoidable selection bias
Mokkala K, et al (2017)	Finland	19	first trimester	Serum zonulin	24-28 weeks	Serum zonulin was associated with higher odds of GDM	Author reported that there is no bias.
Kumru P, et al (2016)	Turkey	19	first trimester	SHBG, HOMA, HbA1c, and cholesterol panel	24-28 weeks	HOMA, SHBG, TG, and LDL-C levels were independent predictors for the development of GDM in low-risk pregnancies	NR
Zhu Y, et al (2016)	America	18	10–14 week	Insulin-like growth factor (IGF)	27 weeks	A significantly increased risk of GDM was an association with higher concentrations of IGF-I	NR
Oztas E, et al (2016)	Turkey	19	first trimester	Serum secreted frizzle-related protein-5 (Sfrp-5)	24-28 weeks	Low first-trimester serum Sfrp-5 levels were significantly associated with the increased risk of GDM.	NR
Cheuk Q, et al (2016)	Hong Kong	19	first trimester	PAPP-A	28-30 weeks	PAPP-A multiple of the median was not predictive of GDM.	Different aboratories may have introduced bias in the assessment of the association between these biochemical markers and GDM.
Wang C, et al (2016)	China	21	first trimester	TG, LDL-C/HDL-C and TG/HDL-C and FPG,	24-28 weeks	Fasting glucose and lipid profiles were potential markers for the prediction of GDM	Group classification errors are possible due to recall bias
Schneuer FJ, et al (2014)	Australia	20	first trimester	25(OH) Vit D	Late pregnancy	Low 25(OH) VitD serum was not associated with GDM	NR
Makgoba M, et al (2011)	UK	18	first trimester	25(OH) Vit D	28 week	did not find evidence of an association between levels of 25-OH- Vit D and subsequent development of GDM	NR
Savvidou M, et al (2011)	UK	21	11+0–13+6 weeks	25(OH) Vit D	24-28 weeks	The serum levels of Vit D were not altered in mothers with type 2 diabetes, those who develop GDM	NR
Baker AM, et al (2012)	North Carolina	20	first trimester	25(OH) Vit D	24-28 weeks	vitamin D deficiency was not associated with GDM.	women who provided serum samples as part of routine prenatal screening, reduced selection bias.
Yeral MI, et al (2014)	New York	19	first trimester	FPG	24-28 weeks	FPG measurement was not appropriate as a screening test for GDM	NR

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Author (year)	Country	Strobe Score	Weeks of Gestation when Measured	Applied Screening Tests	Time of diagnosis	Results	Risk of bias Reported by authors
Hughes RC, et al (2014)	New Zealand	21	first trimester	HbA1c	24-28 weeks	HbA1c ≥5.9% identified all women with diabetes	Treatment for GDM could introduce bias by modifying pregnancy outcomes.
Behboudi-Gandevani S, et al (2013)	Iran	20	14-20 week	iron/zinc serum	24-28 weeks	High serum iron in early pregnancy could increase the risk of GDM	NR
Ferreira AFA, et al (2011)	UK	21	11-13 week	Visfatin and adiponectin	24-28 weeks	Adiponectin is decreased and visfatin is increased could increase the risk of GDM	NR
Caudana AEL, et al (2011)	Mexico	19	First trimester	fasting glycemia, insulin and HOMA	24-36 weeks	Fasting glycemia was the best-adjusted predictor of GDM	NR

NR: Not Reported

Study design and settings

Most of the studies (n= 34) used prospective cohort design. Out of these, five studies had a case-control design. Also, five studies had a nested case-control design. Moreover, four longitudinal cohort designs and thirteen retrospective cohort studies were also included. The studies in different countries included: Turkey (10), China (7), India (2), Iran (2), Italy (5), Sweden (1), UK (8), Sudan (1), Russia (1), Finland (2), Israel (1), Austria (2), Thailand (1), Denmark (1), Mexico (1), Ireland (1), Sain (1), Hong Kong (1), Vienna (1), Santiago de Chile (1), Scandinavian (1), Switzerland (1), Pennsylvania (1), New Zealand (1), North Carolina (1), and New York (1).

Sample size

A total of 161954 high-risk pregnant women in terms of GDM and healthy women were examined in 60 reviewed articles.

Applied diagnostic tests

Many tests were assessed in the first trimester of pregnancy to predict GDM. The most frequently used markers in the reviewed studies were pregnancy-associated with plasma protein (PAPP-A) (in twelve studies); free beta-human chorionic gonadotropin (β -hCG) (in seven studies); lipid profiles and fasting plasma glucose (FPG) (each one in six studies); SHBG (in five studies); hs- CRP, adiponectin, glycosylated hemoglobin (HbA1c) and HOMAand protein-5 (each one in three studies); and insulin growth factor, insulin sensitivity, t-PA, and zonulin, (in two studies). In addition, the other tests were used in only one study. Table 2 summarizes the result of the selected studies according to different applied diagnostic tests.

Discussion

PAPP-A and hCG are used as first-trimester screening biomarkers for trisomy 21 at 11–14 weeks of gestation, which are considered effective screening programs (18). In our study, after reviewing ten cohort studies and a total of 31622 high-risk pregnant women, the low first-trimester incidence of PAPP-A was significantly associated with GDM risk. However, three cohort studies indicated that the low first trimesters of PAPP-A were not associated with GDM risk (8,19). Although the sensitivity or specificity of PAPP-A alone for the prediction of pregnant women at the risk of GDM in these studies was suboptimal. The PAPP-A test alongside other biochemical biomarkers with higher predictive power for the diagnosis of GDM should be assessed in future studies. In our review study, three cohort studies showed that free β -hCG levels had no significant relationship with GDM (20-22). It is not evident whether or not trimester measurements of free β -hCG screening

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Table 2. Summarized the result of selected studies according to different applied diagnostic tests.

Diagnostic Tests	Related studies	Results
PAPP-A	(7,9,16,18-20,22, 68,72,76)	Low PAPP-A was associated with gestational diabetes
	(14,15,17)	Lower PAPP-A was NOT associated with gestational diabetes
free β -hCG	(20-22)	Reduced. free B hCG were associated with GDM
	(15-19)	No significant differences in serum levels of free β -hCG between the two groups
25(OH) Vit D	(59,61,62)	Low 25(OH) Vit D serum in the first trimester of pregnancy were not associated with GDM
hs-CRP	(40,41,67)	hs-CRP levels was correlated with GDM
	(42)	hs-CRP was not correlated with GDM
Fasting Plasma Glucose (FPG)	(27,41,55,70,83)	FPG predicted of GDM
	(38)	FPG measurement is not appropriate as a screening test for GDM in low risk
Total cholesterol (TC), triglycerides (TG), high-density lipid cholesterol (HDL-C), and low-density lipid cholesterol (LDL-C)	(5,6,26,27,52)	Lipid profiles were potential markers for the prediction of GDM
HbA1C	(6,47,49)	Higher HbA1C was associated with gestational diabetes
	(81)	Higher HbA1C was NOT associated with GDM in low-risk women
Insulin sensitivity	(54,55)	Hyperinsulinemia predicted the development of GDM
Insulin-like growth factor (IGF)	(5,84)	A significantly increased risk of GDM in association with higher IGF-I
Leptin- adiponectin- Visfatin	(30,33,36,67)	Could increase the risk of gestational diabetes
Glycosylated fibronectin	(67)	Glycosylated fibronectin is a potential biomarker for the early identification of women at risk for GDM.
tissue plasminogen activator [t-PA]	(5,52)	Predictors of GDM
SHBG	(6,30,43,79)	Decreased SHBG concentrations predict of GDM
	(5)	Not predict of GDM
PROK1	(9)	Lower PROK1 levels are associated with the development of GDM
Hyperemesis gravidarum	(66)	Higher in the hyperemesis predictive of GDM
Total testosterone	(74)	Cannot be used as a marker alone.
Hemoglobin levels	(65)	Higher hemoglobin levels were at an increased risk of developing GDM
Zonulin	(57,58)	Elevated zonulin a good predictor of GDM.
HOMA	(5,6,45)	Predict of GDM development
Iron	(8)	High maternal serum iron could increase the risk of GDM
Three proteins; afamin, serum amyloid P-component - vitronectin	(73)	Elevated afamin, serum amyloid P-component, and vitronectin were confirmed as predictors of GDM
Fatty acid-binding protein-4	(10)	Higher fatty acid-binding protein 4 concentrations were associated with increased risk of GDM
Serum uric acid levels	(11)	Predict GDM development
75 g OGTT	(64)	Was not suitable to be used as a diagnostic or screening test to diagnose the women who are likely to develop GDM
GTT	(78)	Effective diagnosis of GDM by lowering the GCT and GTT plasma glucose cutoffs
Fetuin-A	(41)	Reduced fetuin-A, can be used for the early detection of GDM
irisin	(70)	Reduced plasma levels of irisin were associated with the increased risk of GDM
1,5 Anhydroglucitol	(30)	1,5 Anhydroglucitol is a potential early novel biomarker for the later onset of GDM
Sfrp-5	(71)	Decrease serum secreted frizzle-related protein-5 (Sfrp-5) was associated with the increased risk of GDM
Soluble human leukocyte antigen-G (sHLA-G)	(68)	sHLA-G is an independent marker of GDM
Follistatin-like-3 (FSTL3)	(79)	Follistatin-like-3 (FSTL3) was not significantly different between GDM and normoglycemic pregnancies
higher arginine and glycine and 3-hydroxy isovalerylcarnitine	(72)	There are significant differences in the serum levels of arginine, glycine, and 3-hydroxy-isovalerylcarnitine between controls and GDM groups.
PAPP-A2	(75)	Increased PAPP-A was associated with gestational diabetes

biomarkers are associated with the next risk of GDM (8,9).

Our review findings showed that the first trimester elevations of TG and LDL-C were

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useful markers for the prediction of GDM, and the predictive value of these factors significantly increased along with BMI (10,11). Also, a study showed that TG, LDL-C, and fasting glucose levels were potential markers for the prediction of GDM (10) a meta-analysis evaluated the relationship between lipid measures during pregnancy, and GDM showed that TG was significantly elevated among pregnant women with GDM (23). Adiponectin is primarily expressed and synthesized in maternal adipose tissue and decrease during normal pregnancies (24). In our review, Corcoran et al. (2018), in their cohort study, showed that adiponectin measured in the first trimester of pregnancy was better in the prediction of GDM compared with CRP, SHBG (25). Moreover, Iliodromiti et al. (2016), in their meta-analysis study, reported that the first-trimester adiponectin in isolation had a medium predictive accuracy for GDM (12). Early pregnancy adiponectin may facilitate early recognition of the maternal risk of GDM.

In our review, FPG appeared as a useful predictor of GDM among high-risk women. In the study by Zheng et al. (2019), it was concluded that higher FPG could be used for stratifying the pregnant women with a higher risk of GDM at the beginning of pregnancy (11). However, Wang et al. (2016) showed that FPG appeared as the most accurate predictor of GDM compared with lipid profiles (10).

High hs-CRP has recently been suggested as a predictor for GDM in pregnancy. Serum hs-CRP increased in response to inflammatory repercussions owing to insulin resistance that was seen in GDM (26). Ozgu et al. (2015) found that FPG and hs-CRP in the first trimester of pregnancy are associated with later development of GDM, and hs-CRP provided a better specificity and diagnostic odds ratio for the prediction of GDM (27). Celik et al. (2019) also demonstrated that the elevated hs-CRP has better early diagnostic accuracy for GDM compared to fetuin-A and FPG in high-risk women (28). On the contrary, Naser et al. (2019) found that the first-trimester hs-CRP levels were not correlated with the later development of GDM (29).

The serum levels of SHBG were the other serum marker used in the first trimester for predicting the subsequent development of GDM in low-risk pregnancies. Applied in four studies, our evaluation indicated that, SHBG was a predictor for the subsequent development of GDM; however, it exhibited suboptimal sensitivity (6,25,30).

Another serum marker HOMA. HOMA could be used for the prediction of GDM in the first trimester of pregnancy in low risk of pregnant women (6) (31). HbA1C is known as an index for mean plasma glucose over the previous 3 months. HbA1C is primarily used for the diagnosis and management of diabetes and pre-diabetes in the general population (32). AMYLID et al. (2016) showed that women at risk for GDM had higher first-trimester HbA1c levels and values≥ 6.0% are predictive of GDM (33). A recent review reported that there was limited evidence on the use of HbA1c as a screening tool for undiagnosed diabetes during the first trimester of pregnancy (34). As a result, higher first-trimester HbA1c levels could be used for the prediction of GDM in the first trimester of pregnancy in high-risk pregnant women.

The t-PA is released from vascular endothelium, therefore circulating levels of t-PA antigen may be considered as a marker of endothelial dysfunction. In addition, an increased t-PA antigen level is considered to be a perfect feature of the insulin resistance syndrome and is also associated with the inflammatory reaction (35). It can be concluded that high t-PA was independently predictive of GDM in the first trimester of high-risk pregnancy (5,36).

A normal pregnancy is characterized by an increase in insulin levels at 16 - 18 weeks of gestation. The presence of hyperinsulinemia before this gestational age reflects the risk of developing GDM (37). According to our evaluations, Grewal et al. (2011) showed that the first-trimester hyperinsulinemia preceded

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the onset of symptoms between twenty-four and twenty-eight weeks of gestation and would predict the event of GDM with the restricted sensitivity (38). Another study reported that FPG and fasting C-peptide, along with hyperinsulinemia predict the risk of GDM at the beginning of pregnancy (39).

Zonulin is a novel finding in the prediction of GDM and is also a proposed serum marker for intestinal permeability. The increased intestinal penetrance is related to the upregulation of inflammatory markers and also with insulin resistance (40). According to our evaluations, two recently performed studies showed that there was an association between the increased early pregnancy serum zonulin concentration and GDM, which suggested zonulin as a possible predictor for GDM (41,42).

In this review, three cohort studies showed that the Low 25 (OH) Vit D in the first trimester of pregnancy was not associated with GDM risk (43-46). Zhang et al. (2015) in their meta-analyses study indicated that low serum vitamin D levels in the first trimester of pregnancy were correlated with a higher risk of GDM; however, the included studies were not all randomized controlled (47). Future RCTs are needed to clarify the predictive role of vitamin D in GDM.

75 g OGTT, for GDM detection, is generally performed between 24-28 weeks' gestation. In our review, two studies investigated a 75 g OGTT at the first trimester to identify those women who will subsequently develop GDM. A study showed that a 75 g OGTT was not suitable to be used as a diagnostic or screening test for the developed GDM (48). Another study showed that to75 g GTT was appropriate as a screening test compared to FPG for the prediction of GDM in the first trimester (49). However, still there is a debate on the usefulness of this screening test in the first trimester.

The strengths of this study include a broad review of the role of potential biochemical noted in gestational diabetes.

The limitation of this study was the low number of diabetic women available for this discovery phase in some studies. Because of the high heterogeneity of the quantitative data, we were impossible to apply a meta-analysis. Measurement was not the same in all studies and different criteria were used to diagnose gestational diabetes. Also, the other limitation was several articles with different ethnicities that this impact could not be controlled.

Conclusions

This review showed that hs-CRP, FPG, TG, and LDL-C along with maternal BMI in the first trimester were linked to an increased risk of developing GDM. Proinflammatory cytokines including leptin and adiponectin have been confirmed to impair glucose homeostasis in GDM. It is recommended that further well-designed studies by considering the cost-effective advantages of these predictive tests, should be performed.

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Conflict of Interest

The authors of this article do not have any conflict of interest.

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