Biomarkers used in the early prediction of gestational diabetes

Radu Mateescu[1,2], Gabriel Marina[1,2], Antoine Edu[1,2], Gabriela Obilișteanu[3], Mihaela Bujor[1,2], Stelian Conci[1,2], Gabriela Ionescu[4], Marina Antonovici[1,2], Florin Isopescu[1,2], Mihaela Plotogea[1,2], Alexandru Ispas[1,2], Mihnea Edu[1,2]

1. Department of Obstetrics and Gynecology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

2. Department of Obstetrics and Gynecology, "Nicolae Malaxa" Clinical Hospital, Bucharest, Romania

3. Department of Internal Medicine, "Nicolae Malaxa" Clinical Hospital, Bucharest, Romania

4. PhD Student, Department of Obstetrics and Gynecology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

Corresponding author:
Gabriela Ionescu
E-mail: gabriela.ionescu@drd.umfcd.ro

Abstract

Objectives. *The evaluation of maternal biomarkers that can guide us towards an early diagnosis of gestational diabetes, as early as the first trimester of pregnancy, for a better management and to reduce potential adverse effects of gestational diabetes on pregnancy and pregnant women.* ***Methodology.*** *This article reviews research in the specialized literature and aims to highlight how biomarkers, such as fasting glucose, HOMA score, glycated hemoglobin and PAPP-A, can constitute a set of parameters for screening gestational diabetes as early as the first trimester of pregnancy.* ***Results.*** *Women who developed gestational diabetes exhibited higher values of biomarkers compared to patients unaffected by this metabolic imbalance. Diagnosing gestational diabetes in the first trimester of pregnancy requires correlating multiple biological markers. Most studies suggest that none of the markers used alone have a sufficiently high predictive value for screening gestational diabetes in the first trimester. However, their correlation can quantify the risk of developing this condition and provide a clinical clue in routine practice.*

Keywords: *biomarker, insulin, HOMA, glycated hemoglobin, OGTT, PAPP-A, gestational diabetes, ADA criteria, ACOG criteria*

Rezumat

Obiective. *Evaluarea biomarkerilor materni care ne pot ghida către un diagnostic precoce al diabetului gestațional, încă din primul trimestru de sarcină, pentru un management mai bun și pentru reducerea potențialelor efecte adverse ale diabetului gestațional asupra sarcinii și femeilor însărcinate.* ***Metodologie.*** *Acest articol trece în revistă cercetările din literatura de specialitate și își propune să evidențieze modul în care biomarkeri precum glicemia à jeun, scorul HOMA, hemoglobina glicată și PAPP-A pot constitui un set de parametri pentru screeningul diabetului gestațional încă din primul trimestru de sarcină.* ***Rezultate****. Femeile care au dezvoltat diabet gestațional au prezentat valori mai mari ale biomarkerilor în comparație cu pacienții neafectați de acest dezechilibru metabolic. Diagnosticul diabetului gestațional în primul trimestru de sarcină necesită corelarea mai multor markeri biologici. Cele mai multe studii sugerează că niciunul dintre markerii utilizați singuri nu are o valoare predictivă suficient de mare pentru screeningul diabetului gestațional în primul trimestru. Cu toate acestea, corelarea lor poate cuantifica riscul de a dezvolta această afecțiune și poate oferi un indiciu clinic în practica de rutină.*

Cuvinte-cheie: *biomarker, insulină, HOMA, hemoglobină glicată, TTGO, PAPP-A, diabet gestațional, criterii ADA, criterii ACOG*

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Biomarkeri utilizați în predicția timpurie a diabetului gestațional

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Introduction

With the increasing incidence of obesity in the general population, the incidence of gestational diabetes mellitus (GDM) has followed a similar upward trend, being associated with multiple perinatal complications. The history of medicine reveals the recognition of gestational diabetes as a pregnancy complication as early as 1873[1]. In 1910, a differentiation was proposed between patients who had glycosuria before pregnancy and those who developed glycosuria during pregnancy. From these early cases, the distinction between preexisting diabetes and gestational diabetes was acknowledged. The first studies on carbohydrate metabolism during pregnancy were initiated in 1946[2].

Pregnancy represents a diabetogenic state, and insulin resistance often increases during the third trimester. Gestational diabetes occurs when pancreatic function does not compensate for insulin resistance. It was believed that diabetogenic hormones (growth hormone, corticotropin-releasing hormone, human placental lactogen, and progesterone) secreted by the placenta induce this pathology. Placental growth hormone increases insulin resistance to facilitate fetal nutrition. Additionally, human placental lactogen and prolactin stimulate the mother's appetite by increasing resistance to leptin and promote the proliferation of maternal pancreatic beta cells, leading to insulin production to defend against the development of gestational diabetes[3].

Fetal exposure to an abnormal intrauterine environment, such as a pregnancy with GDM, can impact fetal programming, increasing the risk of developing the metabolic syndrome characterized by diabetes, obesity and, importantly, hypertension throughout life[4]. This is why numerous efforts have been made to break this vicious cycle.

Currently, the universally accepted screening for gestational diabetes is the glucose tolerance test performed between 24 and 28 weeks of pregnancy.

Materials and method

This article aims to highlight the possibility of using alternative biomarkers for the screening and early detection of gestational diabetes mellitus as early as the first trimester of pregnancy. The goal is to detect changes in a clinically silent phase of GDM and prevent subsequent complications.

The inclusion criteria were:

- a single fetus pregnancy
- gestational age less than 14 weeks confirmed by ultrasound
- the informed consent from the patient.

The exclusion criteria were:

- a history of diabetes or insulin resistance (preconception history of altered insulin levels or carbohydrate intolerance in a glucose challenge test)
- use of metformin one month before pregnancy
- fasting blood glucose >105 mg/dL or
- basal blood glucose >200 mg/dL in the first trimester
- alcohol or drug abuse
- active mental illness.

In the studies, serum concentrations of insulin[5], BMI, PAPP-A, cholesterol, high-density lipoproteins (HDL), low-density lipoproteins (LDL) and very-low-density lipoproteins (VLDL) were determined according to the manufacturer's instructions. Homeostatic Model Assessment (HOMA) was calculated using the Matthews formula [insulin (μU/mL) × glucose (mmol/L)/22.5]. Blood glucose concentration and total blood glycosylated hemoglobin were quantified.

Pregnant women at high risk of gestational diabetes[6-14]

The pregnant women with one of the following characteristics seem to have a higher risk of developing GDM. The risk varies depending on these characteristics, and it is additive when multiple risk factors are present.

- Personal history:
  - ✔ GDM in a previous pregnancy (associated with a 40% recurrence risk)
  - ✔ Altered glucose tolerance
  - ✔ HbA1c ≥5.7%
  - ✔ Elevated fasting blood glucose.
- Family history of diabetes, especially in a first-degree relative.
- Preconceptional Body Mass Index (BMI) ≥30 kg/m^2 or significant weight gain at the beginning of adulthood or between pregnancies, or excessive weight gain in the first 18 to 24 weeks of pregnancy.
- Medical conditions associated with the development of diabetes mellitus – e.g., polycystic ovary syndrome (PCOS).
- Advanced maternal age (≥35 years old).
- Member of an ethnic group with a high prevalence of type 2 diabetes such as: Hispanic Americans; American Indians, Alaska Natives, or Native Hawaiians; South Asian or East Asian, Pacific Islanders.
- Previous birth of a child ≥4000 g.

Unrecognized and untreated hyperglycemia in the early stages of pregnancy is important because it is associated with an increased risk of spontaneous abortion and congenital anomalies. Additionally, a number of other unrecognized maternal comorbidities, such as nephropathy or retinopathy, can have serious maternal and obstetric consequences. If these patients are identified early in pregnancy, they could benefit from diagnostic and therapeutic interventions routinely provided to pregnant women with preexisting (pregestational) diabetes.

Early pregnancy screening (universal screening through HbA1c)

Checking the HbA1c level as part of routine prenatal tests can detect gestational diabetes mellitus even from the first prenatal visit.

Other approaches in early pregnancy screening

Targeted screening of individuals at high risk. The International Association of Diabetes and Pregnancy Study Groups (IADPSG)[18], the American Diabetes Association (ADA)[15], and The American College of Obstetricians and Gynecologists (ACOG)[16] – suggest directing early pregnancy screening towards individuals at high risk of undiagnosed type 2 diabetes. However, ADA also suggests physicians consider testing all individuals for undetected diabetes at the first prenatal visit (or before conception). In contrast, a recommendation from the U.S. Preventive Services Task Force (USPSTF) concluded that the available evidence is insufficient to assess the balance of benefits and risks of screening asymptomatic pregnant individuals for glucose intolerance before the 24th week of gestation[5].

ADA and ACOG define patients at high risk for type 2 diabetes based on:

- GDM in a previous pregnancy.
- Preconceptional BMI ≥25 kg/m^2 (≥23 kg/m^2 for Asian-Americans), plus one or more of the following:
  - ✔ first-degree relatives with diabetes
  - ✔ high-risk race/ethnicity (e.g., African American, Latino, American Indian, Asian American, Pacific Islander)
  - ✔ history of cardiovascular diseases
  - ✔ hypertension (≥130/80 mmHg before pregnancy) or treatment for hypertension
  - ✔ HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or triglyceride level >250 mg/dL (2.82 mmol/L)
  - ✔ polycystic ovary syndrome (PCOS)
  - ✔ physical inactivity
  - ✔ other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans).
- Glycated hemoglobin ≥5.7% (39 mmol/mol), impaired glucose tolerance (glucose level at two hours between 140 and 199 mg/dL), or modified fasting glucose (glucose level between 100 and 125 mg/dL) in a pregestational 75-gram oral glucose tolerance test (OGTT).
- HIV infection or exposure to high-risk medications or a history of pancreatitis.
- Age ≥35 years old.

In a randomized clinical study, screening for diabetes during pregnancy due to the presence of obesity (BMI ≥30 kg/m^2) did not demonstrate a reduction in potential adverse effects (e.g., macrosomia, primary caesarean section, pregnancy-induced hypertension, shoulder dystocia, neonatal hyperbilirubinemia, or hypoglycemia)[19].

Directing screening toward symptomatic patients is not useful because many patients are asymptomatic or have unrecognized mild symptoms. However, those with random blood glucose values ≥200 mg/dL (11.1 mmol/L) may experience symptoms of hyperglycemia (e.g., polydipsia, polyuria, weight loss, blurred vision).

The choice of screening test

No approach has been validated for diagnosing diabetes in the first or second trimester of pregnancy. Clinical practice varies depending on the institution and clinician preference. Screening may involve a single A1C, a single fasting blood glucose, a 75-gram oral glucose tolerance test (OGTT) for two hours, or a two-step test (a 50-gram OGTT for one hour followed by a 100-gram OGTT for three hours if the 50-gram OGTT is positive).

If a two-step test is used, we will present the ACOG criteria for diabetes. These criteria are the same as those used for diagnosing gestational diabetes mellitus (GDM) later in pregnancy[20].

Management of patients after an altered early pregnancy OGTT

The benefit of treating a patient whose early pregnancy oral glucose tolerance test meets the ADA criteria for gestational diabetes has not been established. A randomized clinical study, involving over 800 pregnant participants with an abnormal OGTT at the two-hour mark with 75 grams of oral glucose solution before 20 weeks of gestation, compared immediate treatment with retesting between 24 and 28 weeks and initiating treatment for abnormal results.

The immediate treatment of patients who meet the diagnostic criteria for GDM in the early stages of pregnancy did not lead to a clear or significant reduction in births of large-for-gestational-age infants, pregnancy-induced hypertension, or other adverse effects[5].

HOMA+BMI

Ozcimen et al. reported that gestational diabetes can be predicted in the first trimester if the HOMA-IR score is higher 2.60[23]. The predictability for the development of gestational diabetes increased when BMI, waist-to-hip ratio, and weight gain in the first trimester were added and combined with HOMA-IR. Controlling weight gain reduces the incidence of gestational diabetes in pregnant women with elevated BMI and HOMA-IR at the

Table 1 Glucose tolerance test procedure in pregnancy

First step
1. Administer 50 grams of glucose solution regardless of the time of day.
2. Measure plasma or serum glucose levels one hour after administration.
3. A plasma glucose level greater than 135 mg/dL (7.5 mmol/L) or a serum glucose level greater than 140 mg/dL (7.8 mmol/L) is considered elevated and requires the 100-gram glucose tolerance test.
Second step
1. Measure fasting blood glucose level or serum glucose concentration.
2. Administer 100 grams of oral glucose solution
3. Measure plasma or serum glucose levels at one, two, and three hours after administration.
4. A positive test is defined by a high glucose level at two or more time points.

Table 2 Diagnostic values for gestational diabetes

ADA criteria for diagnosing GDM in early pregnancies	Plasma/serum glucose level: mg/dL (mmol/L) during the 75-gram oral glucose tolerance test
à jeun	92 (5.1)
1 hour	180 (10)
2 hours	153 (8.5)

first prenatal visit. In this study, gestational diabetes was predicted in the first trimester with a sensitivity of 80% and a specificity of 58% in pregnant women with a BMI>25.95 kg/m^2 at the first prenatal visit, consistent with other studies[3].

Catalano et al. demonstrated the progressive deterioration of insulin sensitivity in obese women (47%) and in women with normal weight (56%) during the third trimester. Before these gestational weeks, hyperinsulinemia as an independent state of pregnancy may indicate a risk of gestational diabetes[24]. Insulin resistance cannot be measured through a standardized test. Many studies have used HOMA-IR or HOMA, based on the glucose-insulin ratio[25,26]. In conclusion, HOMA-IR and the insulin sensitivity check index have been recommended, but there is no universally accepted threshold for HOMA-IR. We determined the predictability of gestational diabetes with a sensitivity of 90% and a specificity of 61% through ROC analysis in patients whose HOMA-IR scores were higher than 2.08 in the first trimester[3].

Although the studies had some limitations, they showed that gestational diabetes can be predicted using first-trimester data, such as elevated BMI and HOMA-IR values. We can conclude that gestational diabetes can be detected in the first trimester using anthropometric measurements and HOMA-IR. To date, this study is the first to suggest threshold values for HOMA-IR, BMI, and weight gain in the first trimester for gestational diabetes. The main conclusion of this study is that pregnant women with a BMI>25.95 kg/m^2, HOMA-IR>2.08, and weight gain above 4.7 kg are considered at high risk for gestational diabetes[27].

PAPP-A

Pregnancy-associated plasma protein-A (PAPP-A) is a high molecular weight metalloproteinase which, in low quantities, is associated with the presence of fetal Down syndrome. However, its performance as a screening marker gradually decreases with the advancement of gestational age from 9 to 13 weeks[28]. Studies also indicate that low PAPP-A levels may suggest an increased risk for spontaneous abortion, low birth weight, intrauterine growth restriction, preeclampsia, premature rupture of membranes, or placental abruption[29,30].

Recent observations have noted that the presence of low levels of pregnancy-associated plasma protein-A in the first trimester is correlated with the later development of gestational diabetes[31].

Study results demonstrate a connection between serum PAPP-A levels in the first trimester and gestational diabetes, but with moderately predictive outcomes. PAPP-A, produced in the placenta and decidua, acts as a protease controlling insulin-like growth factor (IGF) in relation to insulin-like growth factor-binding protein (IGFBP). PAPP-A breaks down IGFBP, thus low PAPP-A levels lead to an increased amount of IGFBP, causing a decrease in IGF. Insulin-like growth factor promotes the absorption of amino acids and glucose in the trophoblast and acts as an autocrine and paracrine regulator of trophoblastic invasion into the decidua. Therefore, low PAPP-A levels may worsen placental conditions and contribute to the occurrence of adverse effects. Additionally, low IGF levels promote increased circulating insulin, insulin resistance, and abnormal glucose clearance[32].

A meta-analysis of over 300 specialized articles using PAPP-A as a biomarker for predicting gestational diabetes revealed an average sensitivity of 55% (53-58%) and a specificity of 90% (89-90%). The conclusion of this meta-analysis was that low PAPP-A in the first trimester of pregnancy has low predictive accuracy for gestational diabetes. However, this variable can be useful in combination with other tests. Gestational diabetes is a silent condition with few specific symptoms, making PAPP-A levels a potential clue in clinical practice[32].

Conclusions

Although testing for gestational diabetes in weeks 24-28 of pregnancy remains a cornerstone for diagnosing this condition, as we have seen before, studies indicate that an earlier diagnosis can prevent potential complications for both the fetus and the mother.

Diagnosing gestational diabetes in the first trimester of pregnancy requires correlating several biological markers. As mentioned earlier, most studies attest that none of the markers used individually has a predictive value high enough for first-trimester gestational diabetes screening. However, their correlation can help quantify the risk of developing this condition and provide a clinical clue in routine practice. ■

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