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Evaluation of Mild Hyperglycemia During Early Pregnancy

REVIEW
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ABSTRACT

Hyperglycemia and its association with adverse pregnancy outcomes have been comprehensively described in the literature. Moreover, researchers have just about reached a consensus regarding the diagnostics and intervention algorithms for hyperglycemia after the 24th week of pregnancy. However, diagnostic thresholds and intervention algorithms remain controversial during the early pregnancy period. Hyperglycemia, especially during the organogenesis period, may promote serious adverse fetal outcomes like congenital malformations. In this regard, several guidelines have released varying recommendations. We aimed to summarize the current literature regarding the evaluation of mild hyperglycemia during the early pregnancy period. Patients diagnosed with diabetes mellitus in the first trimester based on internationally accepted diagnostic criteria for the general population are beyond the scope of the current article.

Keywords: Diabetes, embryopathy and hyperglycemia, first trimester hyperglycemia, gestational diabetes, hyperglycemia and early pregnancy

Introduction

The increase in the prevalence of diabetes mellitus (DM), especially in pregnancy, has remained concerning. According to the International Diabetes Federationreport, 16.7% of all pregnancies worldwide among women between the ages of 20 and 49 years are complicated by DM. This suggests that DM affects 1 in 6 women during pregnancy.[1] Among patients suffering from DM during pregnancy, gestational DM (GDM) accounts for 80.3%, whereas pregestational DM (PGDM) accounts for 10.6%. The remaining 9.1% comprise patients with undiagnosed DM that was initially identified during pregnancy.[1] Gestational DM has been defined as any degree of glucose intolerance detected during pregnancy for many years.[2] This definition has serious limitations given that it does not distinguish between glycemic disorders occurring due to hormonal changes during pregnancy and those initially detected during the first trimester but were probably present before.[3] The established contemporary definition of GDM is DM diagnosed by the second trimester or later that was not present before pregnancy.[3] The prevalence of DM among women of reproductive age has been rising due to the growing obesity and DM epidemic. This has also promoted an increase in the number of women with undiagnosed DM during their first trimester of pregnancy.[4,5]

Researchers have just about reached a consensus regarding the diagnosis and intervention algorithms for hyperglycemia after the 24th week of pregnancy. However, the early pregnancy period's diagnostic thresholds and intervention algorithms remain controversial. We aimed to summarize the current literature on the diagnosis of, outcomes of, and treatment approaches to mild hyperglycemia in patients who were not diagnosed with DM or prediabetes before pregnancy and were initially evaluated during their first trimester of pregnancy.

We selected articles from the electronic databases "PubMed" and "Google Scholar" by searching the following terms: "early pregnancy hyperglycemia," "first-trimester fasting plasma glucose," "diabetic embryopathy," "diabetic fetopathy," "gestational diabetes mellitus," "hyperglycemia and pregnancy outcomes,", "first trimester hyperglycemia and "pregnancy outcomes," "early pregnancy hyperglycemia," "HbA1c in early pregnancy," and "predictors of gestational diabetes mellitus." Furthermore, current guidelines on this issue were searched individually and cited when relevant. Case reports, comments, abstracts only, and conference papers were excluded. We reviewed the full texts of all articles included in the study.

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Fetal Complications of Maternal Hyperglycemia

The first trimester of pregnancy is when organogenesis takes place and is, therefore, the period in which the fetus is most vulnerable to environmental exposure.[6] Preexisting maternal DM increases the risk of major congenital malformations, spontaneous abortion, stillbirth, and perinatal mortality, especially if strict glycemic control has not been achieved before conception and during pregnancy.[7] Observational data suggest that glycemic control starting before pregnancy until birth can reduce the risk of congenital malformations and perinatal mortality to levels close to those of pregnancies without maternal DM.[8,9]

Diabetic embryopathy describes the adverse consequences caused by maternal hyperglycemia on embryogenesis and fetal development.[10] Conversely, diabetic fetopathy describes the fetal complications of maternal hyperglycemia during second and third trimester of pregnancy.[11]

Hyperglycemia is a potent teratogen and affects normal embryogenesis and development. Although the entire pathophysiological mechanism of the teratogenicity of hyperglycemia has yet to be uncovered, animal experiments have revealed several pathological mechanisms.[6,10] According to the results of these experiments, maternal hyperglycemia causes embryopathy through oxidative stress, hypoxic stress, increased apoptosis, and altered gene expression.[12,13] Conversely, the main mechanism for diabetic fetopathy is associated with the fetal response to hyperglycemia rather than the direct toxic effect of hyperglycemia on the fetus. Maternal hyperglycemia causes fetal hyperglycemia through placental crossing. Fetal hyperglycemia induces hyperinsulinemia, which consequently triggers pathological processes during the second and third trimester.[11] Fetal hyperinsulinemia contributes to increased metabolic rate, oxygen consumption, fetal hypoxemia, macrosomia, and stillbirth.[14,15] The adverse outcomes of maternal hyperglycemia are summarized in Table 1.[16-18]

All aforementioned data were obtained from observational and retrospective studies examining pregnant women with known preexisting DM or GDM. This article evaluates the diagnosis, management, and clinical outcomes of hyperglycemia in the first trimester of pregnancy among women without a PGDM or prediabetes. Patients diagnosed with DM in the first trimester based on internationally accepted diagnostic criteria of DM for the general population are beyond the scope of the current article.

MAIN POINTS

- High glucose levels during the first trimester, even within the normoglycemic range, are linked to adverse pregnancy outcomes.
- Fasting plasma glucose and HbA1c levels of ≥92 mg/dL and ≥5.9%, respectively, have been linked to poor pregnancy outcomes and the risk of developing gestational diabetes mellitus in women without pregestational diabetes or prediabetes.
- There is limited high-quality information on whether interventions based on these values improve unfavorable pregnancy outcomes in patients without diabetes or prediabetes using standard diagnostic criteria.

Table 1. Adverse Outcomes of Maternal Hyperglycemia

Pregnancy Period	Complication	Condition and Frequency* (%)
First trimester	Diabetic embryopathy	• Spontan abortus (18.6, 25.1)** • Congenital malformations (5-6) • Cardiac (2.5-4) • CNS (0.1-0.5) • Other (gastrointestinal, genitourinary, skeletal, cleft palate etc.) (1-2)
Second and third trimester	Diabetic fetopathy	• Macrosomy/LGA (15-45) • Neonatal hypoglycemia (25-50) • Neonatal hypocalcemia (5-30) • Polycythemia (5-10) • Respiratory problems (5-15) • Asphyxia (1-3) • Hypertrophic cardiomyopathy (10-15) • Perinatal mortality (0.5-2)

CNS, central nervous system; LGA, large for gestational age.
*The frequency data retrieved from studies conducted in women with pregestational diabetes (type 1 or type 2).[16-18]
**Miscarriage occurs in 12% to 15% of recognized pregnancies in the general population. The specified frequencies were obtained from a study conducted in Norway and represent the occurrence rates in women with type 1 and type 2 diabetes, respectively.[18]

Glucose and Glycated Hemoglobin Thresholds Associated with Adverse Outcomes in the First Trimester

Although high glucose levels in early pregnancy are associated with adverse outcomes, no consensus has been established on glucose levels at which risk begins. Several studies have revealed that higher glucose levels during the first trimester, even those within the normoglycemic range, is associated with adverse outcomes.[19-22] Riskin-Mashiah et al[21] retrospectively evaluated the association between first-trimester fasting plasma glucose (FPG) levels and adverse pregnancy outcomes in pregnant women without PGDM, excluding those with first-trimester FPG levels above 105 mg/dL. They analyzed FPG using 7 categories (<75, 75-79, 80-84, 85-89, 90-94, 95-99, and 100-105 mg/dL) similar to the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study.[23] It should be kept in mind that values between 100-105 mg/dL are within the prediabetic range. Accordingly, they revealed that the frequency of large for gestational age (LGA) and macrosomia increased with increasing maternal FPG category and that the association was sustained even after excluding women who developed GDM.[21] Moreover, the same study found that 11.4% of the participants had maternal first-trimester FPG levels >90 mg/dL, with data suggesting that this level identified 12.2% of first cesarean delivery and 17.7% of LGA neonates.[21] In another study, Li et al[24] demonstrated that higher FPG levels in the first trimester are associated with an increased incidence of adverse pregnancy outcomes

Benhalima et al[25] revealed that those with mild hyperglycemia (92-100 mg/dL) in the first trimester had greater neonatal intensive care unit admission rates compared to those with FPG levels <92 mg/dL, even in patients with normal oral glucose tolerance test. Another study showed that women with first-trimester FPG levels between 92 and 124 mg/dL had higher incidences of LGA, primary cesarean, preterm birth, preeclampsia, and neonatal

distress than did those with levels <92 mg/dL. The same study revealed a graded relationship between first-trimester FPG levels (<92, 92-100, 100-124 mg/dL) and preterm delivery rates.[22] Geurtsen et al[26] evaluated the differences in fetal growth rate per 18 mg/dL (1 mmol/L) change in non-FPG levels during early pregnancy in 6111 patients; only 24 reported having preexisting DM. Notably, they reported an increase in the risk of LGA, a decrease in mid-pregnancy growth rates, and an increase in late-pregnancy growth rates with increasing non-FPG levels in early pregnancy.

Glycated hemoglobin, which reflects the average glucose levels of the previous 2-3 months, is expected to be lower in pregnant women than in non-pregnant women due to increased erythrocyte turnover during pregnancy, especially during the second and third trimesters.[3] Evaluating HbA1c during the first visit may be reasonable to obtain information regarding the ongoing glycemic status in patients without known DM. This issue has been addressed in the literature, and the association between first-trimester HbA1c values and adverse pregnancy outcomes in pregnant women without known DM has been scrutinized. Notably, a retrospective study on 16 122 pregnant women by Hughes et al[19] revealed that first-trimester HbA1c values ≥5.9% (≥41 mmol/mol) could be a predictor for some adverse outcomes (preeclampsia, major congenital anomaly, shoulder dystocia, and perinatal death).[19] Similarly, Mañé et al[27] revealed that patients with HbA1c levels ≥5.9% in their first trimester had an approximately 3 times higher risk for preeclampsia and macrosomia than did those with HbA1c levels <5.9%, regardless of GDM diagnosis in the 24th-28th week of pregnancy. In both studies, those with known PGDM and those diagnosed with DM according to standard diagnostic criteria in the first trimester were excluded. In a subsequent study, Mañé et al[27] concluded that FPG was not superior to HbA1c in predicting adverse pregnancy outcomes during the early pregnancy period. Moreover, they reported that first-trimester levels of HbA1c of 5.8% and higher were associated with macrosomia.[28]

The majority of the studies revealed that the rate of adverse pregnancy outcomes increases with higher first-trimester FPG levels, even within the normoglycemic range.[19-22,24] The FPG and HbA1c thresholds for increased risk of adverse pregnancy outcomes seem to be 92 mg/dL and 5.9%, respectively.[19,22,25,27] However, it remains controversial whether intervention at this level reduces the risk for adverse pregnancy outcomes. A non-blinded randomized clinical trial compared treatment (medical nutritional therapy and pharmacotherapy if needed) of mild hyperglycemia (fasting glucose ≥92 mg/dL and/or HbA1c ≥5.7%) beginning in the first trimester to that at the 28th week of gestation. Accordingly, the study found that early treatment did not improve neonatal and maternal outcomes. However, one should note that this study was underpowered and terminated early.[29] In another study, Rowan et al[30] demonstrated that early intervention reduced the risk of preeclampsia in women with first-trimester HbA1c values between 5.9% and 6.7%. The threshold glucose level at which treatment is required during the first trimester in mothers without PGDM has not been clearly identified. Although several studies have revealed that glucose levels above 92 mg/dL during early pregnancy were associated with adverse pregnancy outcomes, limited high-quality evidence has been available regarding whether intervention above this value reduces risk.

Predictive Ability of First Trimester Glucose Levels on Gestational Diabetes Mellitus

Gestational DM is detected by screening at the 24th-28th week of pregnancy in women without PGDM. Gestational DM has been known to be associated with increased adverse outcomes, including LGA, macrosomia, preeclampsia, polyhydramnios, stillbirth, cesarean delivery, and neonatal morbidity.[23,31] A systematic review and meta-analysis conducted by Madhuvrata et al[32] concluded that early dietary intervention has decreased the incidence of GDM in women who have GDM risk factors. Several studies have aimed to develop strategies for predicting subsequent GDM in early pregnancy. Numerous inflammatory markers, peptide levels, markers of insulin resistance, placenta markers, genitourinary tract microbiota, ultrasound markers, and various machine-learning algorithms based on medical records and clinical characteristics related to this matter have been studied.[33-37]

Several studies have investigated first-trimester FPG and HbA1c levels as predictors of subsequent GDM. Riskin-Mashiah et al[38] reported that the risk of GDM increases by approximately 1.5-fold with every 5-mg/dL increase in first-trimester FPG levels, even those within the normoglycemic range. The aforementioned study, which was designed similarly to the HAPO trial, showed that GDM development was strongly associated with first-trimester FPG.[21] Li et al[24] showed that FPG in the first trimester was an independent risk factor for GDM and could be used to predict GDM in Chinese women. Corrado et al[39] reported that first-trimester FPG levels ≥92 mg/dL were highly predictive of GDM.

Besides FPG, the predictive power of first-trimester HbA1c levels for GDM has been investigated in several studies. Accordingly, a study conducted by Mañé et al[27] found that the prevalence of subsequent GDM was 46.8% and 11.9% among women with first-trimester HbA1c values ranging from 5.9%-6.4% and <5.9%, respectively. Another study revealed that HbA1c levels in the pre-diabetic range (5.7%-6.4%) during the first trimester predicted GDM with a specificity and sensitivity of 94% and 13%, respectively.[40] The majority of studies revealed that the probability of GDM diagnosis between the 24th and 28th week increased in women with a first-trimester HbA1c level of ≥5.9%. In a systematic review by Kattini et al,[41] high HbA1c starting from the value of 5.7% was associated with a higher risk of subsequent GDM, and the risk increased as the HbA1c value got closer to 6.5%.

Summary of Guidelines Relevant to Hyperglycemia Treatment In the Early Pregnancy Period

Researchers have just about reached a consensus on treatment and follow-up algorithms for GDM and PGDM during pregnancy. The current guidelines have controversies regarding the diagnosis and intervention for mild hyperglycemia during early pregnancy.

All of the guidelines recommend early screening for hyperglycemia in pregnancy. The standard diagnostic criteria used in non-pregnant individuals are encouraged to be used for the diagnosis of overt diabetes in early pregnancy by most guidelines.[3,42-46] There is a consensus that patients diagnosed with overt diabetes based on standard criteria in the early pregnancy period should be evaluated as PGDM and treatment algorithms should be implemented accordingly. However, different guidelines have various recommendations regarding FPG and HbA1c values below the diagnostic threshold.

American Diabetes Association (ADA) recommends using the threshold 110-125 mg/dL for FPG and 5.9%-6.4% for HbA1c value before the 15th week of gestation to identify women with a higher risk for adverse outcomes and more likely to need insulin therapy.[3] These recommendations appear beneficial in identifying patients likely to necessitate insulin, consequently reducing the workload. However, they do not encompass all patients according to internationally accepted diagnostic criteria for prediabetes. This exclusion may leave out certain individuals who require intervention. Numerous studies indicate that the risk of adverse pregnancy outcomes begins to escalate at a glucose level of 92 mg/dL in the first trimester.[19,22,25,27] Notably, these values are currently not addressed in the recommendations by the ADA. Whereas the Society of Endocrinology and Metabolism of Türkiye (SEMT) recommends individuals diagnosed with prediabetes in the early pregnancy period based on standard diagnostic criteria be treated as overt diabetes.[43] Similarly, SEMT does not point to the FPG value of 92 mg/dL in the first trimester. There is a lack of evidence in the literature supporting the use of an FPG level of 92 mg/dL as the treatment threshold to reduce adverse pregnancy outcomes. This absence of conclusive evidence justifies the omission of this value as an intervention threshold. Nevertheless, we posit that individuals with FPG levels between 92 and 100 mg/dL should not be disregarded, and a patient-centered decision-making approach should be adopted. Unlike the others, The Hellenic Endocrine Society draws attention to taking into consideration FPG levels between 92 and 100 mg/dL in early pregnancy.[44] The Hellenic Endocrine Society recommendations, while encompassing the vast majority of patients at

Table 2. Summary of Guidelines Regarding Diabetes in Pregnancy

Guideline	Recommendations Regarding Early Pregnancy Screening
ADA[3]	• Recommends screening women with risk factors* before 15 weeks of gestation • Recommends considering testing all women for missed diabetes diagnosis if not tested preconceptionally (diagnosis is to be based on standard criteria) • Recommends screening for abnormal glucose metabolism before 15 weeks of gestation. Use the threshold 110–125 mg/dL for FPG and 5.9%-6.4% for HbA1c value to identify women with a higher risk for adverse outcomes and more likely to need insulin therapy.
NICE[47]	• Recommends not using FPG, RPG, HbA1c, OGTT, or urinalysis for glucosuria to determine the risk of subsequent GDM. • Recommends early SMBG or 75 g OGTT as soon as possible for women with a history of GDM. • Recommends screening from the 24th-28th week via 75 g OGTT for women with risk factors* other than the history of GDM. • Recommends making a diagnosis of GDM if FPG >100 mg/dL or 2-h glucose >140 mg/dL.
CDA[42]	• Recommends early screening (before the 20th week) with HbA1c and/or FPG in women at high risk* for PGDM and using standard criteria for diagnosis of PGDM (FPG≥ 126 mg/dL, HbA1c≥ 6.5%).
SEMT[43]	• Recommends screening for FPG at the first prenatal visit. Evaluate using 75 g OGTT in the presence of risk factors, even if FPG is normal, and using standard diagnostic criteria for non-pregnant individuals. Re-test at 24-28 weeks if no glycemic disorder is detected. • Recommends treatment for known PGDM in the presence of overt DM or pre-DM (IFG, IGT, and/or HbA1c between 5.7–6.5%) based on standard diagnostic criteria.
HES[44]	• Recommends screening for FPG at the first prenatal visit. • Recommends lifestyle and dietary measures if FPG is between 92 and 125 mg/dL and re-testing 2 weeks. • Recommends performing 75 g OGTT if FPG is between 92 and 100 mg/dL at the 14th-18th gestational week, and establishing a diagnosis of GDM if FPG is between 101 and 125 mg/dL. • Recommends making a diagnosis of PGDM if FPG > 125 mg/dL, and re-testing at 24-28 weeks of gestation if FPG < 92 mg/dL.
Flemish consensus[44]	• Recommends screening for FPG in case of pregnancy plan or at the first prenatal visit and using diagnostic criteria for non-pregnant individuals. HbA1c may be used as an alternative. • Recommends treatment with a standard diabetes algorithm if overt diabetes (FPG ≥ 126 mg/dL) is diagnosed. • Recommends lifestyle measures if IFG (FPG: 100-125 mg/dL) is diagnosed and re-testing using the 75 g OGTT between 24th and 28th week of gestation. SMBG is not recommended in the case of IFG. • Recommends re-testing between 24th and 28th week if FPG is <100 mg/dL (using the 50 g OGTT if no risk factors are present and 75 g OGTT if BMI is ≥30 and/or the patient has a history of GDM).
Consensus document from Spain[46]	• Recommends testing to rule out overt DM in the first prenatal visit. Use the standard criteria for the diagnosis of overt DM. • Recommends GDM screening for high-risk* women in the first trimester (10-12 weeks) using the 50 g OGTT.
SOGC[48]	• If there is a high risk for GDM based on risk factors*, recommend screening during the first half of pregnancy using the 50 g glucose challenge test or 75 g OGTT. Use the same diagnostic threshold for the 24th-28th week. Re-test between 24th and 28th week if normal.

*Maternal age (>35 years), family history of diabetes, obesity, polycystic ovary syndrome, ethnicity, corticosteroid use, previous gestational diabetes, previous macrosomic infant, and acanthosis nigricans.
ADA, American Diabetes Association; BMI, body-mass index; CDA, Canadian Diabetes Association; DM, diabetes mellitus; FPG, fasting plasma glucose; GDM, gestational diabetes mellitus; HES, Hellenic Endocrine Society; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NICE, National Institute for Health and Care Excellence; OGTT, oral glucose tolerance test; PGDM, pregestational diabetes mellitus; RPG, random plasma glucose; SOGC, The Society of Obstetricians and Gynecologists of Canada; SEMT, The Society of Endocrinology and Metabolism of Türkiye; SMBG, self-monitoring of blood glucose.

risk, also warrant consideration for the substantial increase in the number of patients. On the other hand, the recommendations of the National Institute for Health and Care Excellence (NICE) guideline exclude a considerable number of patients who are at risk of adverse pregnancy outcomes based on current knowledge.[47] The recommendations of several guidelines on this issue are summarized in Table 2.[3,42–44,46–48]

Conclusion

Current research indicates that FPG and HbA1c levels of ≥92 mg/dL and ≥5.9% are linked to negative pregnancy outcomes and increased risk of developing GDM in patients without PGDM. Because FPG levels below 100 mg/dL are defined as normoglycemia based on internationally accepted criteria, FPG levels between 92 and 100 might be termed as "borderline hyperglycemia." The majority of studies show that the risk of GDM and adverse outcomes increases as FPG and HbA1c levels get closer to the diagnostic threshold. These findings suggest that preconception evaluation of childbearing-age women based on risk factors and the establishment of accurate diagnosis are desirable. Therefore, treatment algorithms could be implemented before pregnancy. Unfortunately, this does not always hold true in clinical practice. It seems reasonable to evaluate all pregnant women with FPG and HbA1c at the first prenatal visit. The diagnosis of overt DM can be made based on the diagnostic criteria used in the general population, and therapeutic interventions could be applied to those with a diagnosis of overt DM or prediabetes. This approach refers to recommendations from the SEMT and covers the majority of pregnant women at risk.[43] The decision to treat patients with FPG levels between 92 and 100 mg/dL can be made based on concomitant risk factors.

Well-designed clinical studies are needed to examine the obstetric and neonatal outcomes of treating borderline and mild hyperglycemia during early pregnancy in people without established diabetes.

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