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Review Article

An Updated Review of the Gestational Diabetes

Mozhgan Hafizi Moori*

Department of Midwifery, Faculty of Nursing and Midwifery, Ahvaz Branch, Islamic Azad University, Ahvaz, Iran.

Abstract

High blood glucose levels during pregnancy can lead to unfavorable outcomes in the mother, fetus, and neonatal state. This review focused on the latest guidelines on diagnosis, monitoring, and treatment of gestational diabetes mellites. This narrative review was conducted by searching through several online databases including PubMed, Science Direct, and Embase for relevant articles using keywords such as "Gestational Diabetes", "Diabetes Mellitus", "Pregnancy", and "guideline" with no date limitations. Based on the literature review, proper treatment of diabetes during pregnancy results in a normal pregnancy, labor, postpartum state. The key to a normal pregnancy is to control and keep your blood sugar levels within the recommended range by various guidelines, which were the discussion subjects of this narrative review in detail. In addition to maintaining normal blood sugar levels before or during pregnancy, there should be a balance between diet, exercise, and insulin intake if indicated for treatment. Gestational diabetes control program needs close monitoring and appraisal with progression in the pregnancy. As a result, recognizing the burden of gestational diabetes is decisive for timely diagnosis and further evaluations by healthcare policymakers. Overall, multiple updates on the guidelines of gestational diabetes management are annually published, and a comparison of these guidelines could inform clinicians to update their approach.

Keywords: Gestational diabetes, Hyperglycemia, Insulin, Glucose tolerance test

***Correspondence to**

Mozhgan Hafizi Moori, Department of Midwifery, Faculty of Nursing and Midwifery, Ahvaz Branch, Islamic Azad University, Ahvaz, Iran.

Tel: +989112581083,

Email: academicorespond@gmail.com

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Introduction

Any level of dysglycemia, which is first observed through pregnancy, according to some studies (1, 2), is attributed to gestational diabetes mellitus (GDM). GDM, which has now emerged as a worldwide health issue in nearly all countries (3), causes maternal and fetal death (4). GDM-affected mothers might be more unguarded to the occurrence of hypertension and preeclampsia during the pregnancy and may be at the risk of cesarean delivery (5). These women are much more likely to suffer from diabetes mellitus and cardiovascular disease later in life and their babies are more likely to be macrosomic, to have more congenital abnormalities, and to develop neonatal hypoglycemia and type 2 diabetes mellitus (T2-DM) later in life (6). So far, there have been no definitive criteria for GDM diagnosis. Different policymakers apply distinct medical criteria to find how common it is. GDM is estimated to be present in 7% of the worldwide population's pregnancies (7). Its prevalence ranges from 5.4% to 14.0% in Europe (8) while it varies between 0.7% and 51.0% in Asia (9). Race/ethnicity differences (10), differences in diagnosis (6), and the wide variation in prevalence rates can be explained by screening methods (6) and demographic characteristics (7-9). The Iranian guideline is extracted from the National Institute for Clinical Excellence (NICE), American Diabetes Association, American College of Obstetricians and Gynecology, USPSTF, and International Diabetes Federation (10). Several revisions to the gestational diabetes management guidance are annually released, and a comparative analysis of these recommendations may help clinicians improve their approach. New guidelines have more focused on preconception therapy that can be integrated into normal diabetes treatment beginning at puberty and progressing with both women with diabetes and reproductive ability (11). Based on the American Diabetes Association guideline 2020, family planning must be addressed in preconception counseling, and A1C must be fitted for pregnancy (11).

Materials and Methods

This narrative review was performed by searching through several online databases (i.e., PubMed, Science Direct, and Embase) for relevant articles using keywords such as "Gestational Diabetes", "Diabetes Mellitus", "Pregnancy", and "guideline" with no date limitations. English and Persian studies were considered to compare the Iranian Guidelines with international guidelines. The

results were evaluated and the ones for inclusion based on their relevance to the topic were selected accordingly. This was determined by the participating writers' opinions and agreement. Additional papers were discovered by manually monitoring the reference lists of the included articles.

Results

The results of this narrative review were discussed in areas of diagnosis, classification, screening, diagnostic criteria, management, dietary management, self-monitoring of blood glucose, pharmacological treatment, and insulin and oral agents.

Diagnosis

Even after the current guidelines of GDM management and diagnosis, it is yet unknown when and how a diagnosis of gestational diabetes can be established, what clinical goals should be set, and, most notably, which early care will women benefit from if they are diagnosed with gestational diabetes (12).

The findings of a glucose tolerance test could help in diagnosing GDM. In this method, 75 g sugar is orally used by the patient, and two hours late, her blood level is tested for glucose or 100 g sugar is consumed and blood glucose level tests would be performed three hours later. These tests are known as oral glucose tolerance test (OGTT). The 75-g 2-hour OGTT is another test, and the 100-g 3 OGTT is usually the last step in a two-step test. GDM is diagnosed when one of the 75-g 2-hour glucose values represents an increase. Although there are many diagnostic requirements for GDM, there have been some debates about the best thresholds for a positive result (13-15). Based on the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study, the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) parameters have been the most widely used cutoff rates for adjudication of elevated values (16). In comparison to the 100-g 3-hour test, the 75-g 2-hour test is more realistic and easier. Furthermore, it tends to be more sensitive compared to the 100-g 3-hour test in predicting pregnancy complications such as hypertension-related disorders such as preeclampsia and macrosomia (17). In the two-hour test, only one elevated glucose value is required for GDM diagnosis confirmation while in a three-hour test, two abnormal glucose values in tests should be recorded to confirm the diagnosis (18). The application of glucose tolerancetests is questioned by some researchers (19).

The World Health Organization (WHO) does not currently have such a guideline on whether or how to test for gestational diabetes, but studies to endorse a realistic and efficient screening program are underway. In view of this, early detection of fetal growth acceleration in pregnancy, as well as proof that preventative steps should be taken before 20 weeks of pregnancy can help in guiding schedules to serve as advice for the screening protocols of gestational diabetes and to enhance neonatal outcomes (20).

Based on the Iranian guideline of GDM, all women who do not have known diabetes and come in for the first visit during pregnancy. They should have their serum glucose/fasting plasma measured (at least 8 hours after the last meal) during the past year (universal screening) if their blood sugar is not assessed before pregnancy (10). The diagnosis of diabetes is clearly confirmed if the serum/plasma glucose is more than 200 mg/dL in the presence of the classic symptoms of diabetes or if the fasting serum/plasma glucose is between 100 and 125 mg/dL even at one time. If the screening of pregnant women in the early stages of pregnancy is negative, it is necessary to repeat the two-stage screening between 24 and 28 weeks of pregnancy (10).

Classification

The classification of glucose intolerance disorders, which are happening and have been identified during pregnancy, is required for the epidemiological assessment of the disease and the identification of clinical conditions related to the disease. In previous studies, the WHO described GDM as a metabolic disorder of glucose or glucose intolerance that gets developed through pregnancy. These broad concepts of GDM, which includes a category of "extreme hyperglycemia", are devoid of clear evidence from interventional studies (21, 22). Numerous studies have addressed the connection between the mother's blood glucose levels, as well as the maternal and fetal outcomes. HAPO and Australian Carbohydrate Intolerance Study in Pregnant Women study included no patients with severe hyperglycemia (23). Moreover, Landon et al (24) removed the data related to the fasting blood glucose levels of less than 5.3 mmol/L. The IADPSG (25) coined the word "overt diabetes" to describe a form of extreme hyperglycemia that mimics pre-existing diabetes.

White et al invented a classification scheme for GDM in 1949, and it is now known as the White's classification. They categorized diabetes in pregnancy into A (better) to F (worse) based on the age of diabetes initiation in the mother and diabetes-related complications in the mother (less favorable). Until 1980 (9), the initial White classification was subjected to several changes. The first revision was issued in 1965 when vascular disorders were moved to class D and a new class R was added to indicate the existence of proliferative retinopathy. GDM was considered in class A in 1972 (26). The American College of Obstetricians and Gynecologists (ACOG) found White's scheme to be useless in clinical practice and thus introduced a new classification, which included a note about the occurrence or the lack of metabolic complications (27). All cases of hyperglycemia occurring during pregnancy, as well as GDM and pre-

existing diabetes are currently considered as diabetes in pregnancy. This definition should be considered as a term that includes undiagnosed T2-DM, which is manifested as overt diabetes that is initially diagnosed in pregnancy, and absolute GDM (21-28).

Screening

GDM screening, which began 50 years ago, has shown an increased probability of hyperglycemia through gestation (23-29), along with proof indicating that successful management of this medical condition can minimize adverse outcomes in the mother and the fetus (22, 23-30). However, there was debate about whether GDM screening must be conducted in all pregnancies or just in at-risk mothers.

Accordingly, the early detection of GDM is particularly important in women from populations where T2DM is endemic. On the other hand, early detection of GDM and a higher rate of diagnosis are predicted to increase psychological stress (22-24).

Based on the IADPSG guidelines, GDM screening should be considered for all women at 24-28 weeks of pregnancy with a 2-hour OGTT while compulsive glycemic status assessment in all late pregnancies using this test is still debatable (24). The American Diabetes Association and the American Diabetes Prevention Program (26) advocate for universal screening whereas it is opposed by some other guidelines (30). According to the Scottish Intercollegiate Guidelines Network, women with risk factors should be screened selectively (26). Furthermore, a prior history of GDM was considered as the prerequisite risk factor for early and 24-28 weeks tests (28, 29). Based on the available recommendations, screening during pregnancy should be performed relying on the existence of predisposing factors while these factors are not fully understood yet. A body mass index (BMI) of >30 kg/m^2 as a risk factor for GDM in some studies (22-27) whereas higher (35 kg/m^2) or lower (25 kg/m^2) BMI values are considered as the cutoff in another study (28). Currently, the Iranian working group proposes the use of a two-step method, in which, the GCT test is performed with 50 g of water-soluble anhydrous glucose powder in the first stage (10).

In screened pregnancies by 2-hour OGTT, a retrospective observational analysis was conducted to determine the validity of each recommendation for detecting GDM. The findings revealed that the anthropometric indices of the mother and GDM history were the most sensitive risk factors for GDM. Fewer numbers of women were excused from screening, nearly as if universal screening were employed considering that the proportion of women of reproductive age who would be tested for GDM employing the recommended potential risks of ADA is higher than those recommended by NICE and the ADIPS. Nevertheless, fewer individuals will be screened by following the NICE and ADIPS standards, leading to the negligence of far more females (30).

Diagnostic Criteria

O'Sullivan et al (31) established a GDM clinical definition centered on a 3-hour, 100-g OGTT, that has been applied to predict subsequent diabetes, as well as the risk of increased prenatal morbidity and death in GDM patients (30). Nonetheless, extensive controversies exist about how to define glucose disorders in pregnancy. The presence of multiple diagnostic criteria and blood glucose thresholds for detecting GDM is the primary cause of this diagnostic disagreement.

Management

Women with GDM should seek advice from a dietitian as soon as they are diagnosed to begin medical nutrition therapy, which is the cornerstone of any management strategy (32). The main objective is sufficient weight gain maintenance while maintaining normal glycaemic regulation without ketosis or fetal compromise, as determined by the prenatal BMI (33). In the Iranian guideline, therapeutic goals at this stage of pregnancy do not differ from other times of pregnancy, and fasting sugar reduces to less than 95 mg/dL. One-hour glucose below 140 mg/dL and two-hour glucose below 120 mg/dL are recommended based on weaker evidence. In the case of recurrent hypoglycemia, the above-mentioned targets can be considered higher than 5-10 mg/dL (10). Several studies comparing various types of diets were conducted to identify an acceptable food intake for women with GDM. Obese women with GDM should consume a low-calorie diet according to experts. In a randomized controlled trial, lowering total caloric intake resulted in substantial ketosis in overweight women with gestational diabetes compared to the control group (24). Obese women, on the other hand, should consume more than 25 kcal/kg per day to avoid ketosis and fetal development compromise (27). As a result, the ACOG advises pregnant women, who weigh more than 120% of their normal body weight, to limit their daily calorie intake to around 24 kcal/kg (27). The ACOG also outlined the daily calorie needs, organization, and distribution (27).

Dietary Management

In GDM, paying much attention to the volume and form of dietary carbohydrates is critical. Dietary carbohydrate ranges from basic sugars to longer-chain oligo- and polysaccharides, which together affect blood glucose, microbial metabolism, and bowel activity in different ways. The amount and type of dietary carbohydrate will affect maternal glucose and nutritional status according to new guidelines. The volume and type of dietary carbohydrate will also affect maternal glucose levels, according to studies, and nutritional guidelines encourage women

with GDM to restrict total intake or prefer complex and low glycemic dietary carbohydrates (34).

Exercise has been linked to improved insulin sensitivity in some women with gestational diabetes that can optimize both fasting and postprandial blood sugar levels even without medication (35). When compared to controls, physical activity has been demonstrated to reduce the need for insulin in the management of GDM (36). According to Dempsey et al, exercise reduces the incidence of preeclampsia in women who are pregnant (33). Likewise, a case-control study uncovered that those women having daily physical activity had a 35% reduced risk of preeclampsia compared to women who did not have any physical activities (37). Where there is no medical or obstetrical issue, moderate-intensity physical activity is recommended by the ADA as half of every treatment strategy (24).

In the Iranian guideline, the use of exercise in all patients with gestational diabetes, if not prohibited, can delay the consumption of drugs in these patients or eliminate or reduce the need for it to some extent. In these cases, aerobic exercise is more useful. However, endurance sports can be applied as well. The duration of daily exercise is at least half an hour with moderate intensity and at least 4-5 days a week. In people who are not physically fit, it is better to start exercising a quarter of a day and gradually increase it to reach the desired time (10).

Self-monitoring of Blood Glucose

Physical exercise and medical nutrition therapy are recommended after the diagnosis of GDM. Additionally, repeated self-monitoring of blood glucose is needed to track the pregnant woman's glycaemic regulation and decide if it is sufficient or whether pharmacological therapy is required in this regard (31). The use of regular self-monitoring of blood glucose has been linked to a lower probability of negative outcomes (31). In insulin-treated women, frequent self-monitoring of blood glucose focused on postprandial rather than preprandial monitoring is superior in improving glycaemic control (31) while it is doubted by some researchers (32). Continuous glucose monitoring (CGM) is a new technology that allows for 24-hour glucose monitoring. A recent prospective study among Chinese women with GDM demonstrated that using CGM technology improved glycaemic regulation while reducing the risk of adverse outcomes when compared to controls (33).

Pharmacological Treatment

Pharmacological care should be started if nutritional therapy fails to keep women with GDM on track. Although human insulin is usually the first choice, insulin analogs and some oral agents may be used as well (38). Insulin is typically applied when glycemic thresholds are surpassed although some randomized trials have suggested that insulin should be started solely based on fetal ultrasonic parameters such as increased fetal abdominal girth (34). Tarry-Adkins et al (39) have recently published a meta-analysis indicating that insulin therapy could reduce the birth of neonates diagnosed large for gestational age (LGA) and fetal macrosomia significantly. Further, when fetal growth is normal, ultrasound-guided management has been shown to minimize the need for insulin care, lowering the risk of small for gestational age (40).

The International Association of Diabetes in Pregnancy Study Groups guidelines claims that treating GDM reduces perinatal mortality (41).

American Diabetes Association has proposed a guideline for GDM for the role of oral agents of glucose management in GDM mothers. Although glyburide was once considered a better solution to insulin than metformin, a 2015 meta-analysis and systematic study demonstrated that it was related to a greater risk of neonatal hypoglycemia and macrosomia compared to either insulin or metformin (42). The corresponding ADA recommendations (43) downplayed its role in the management of GDM based on the new evidence. According to the Iranian protocols, oral medications, especially metformin, can be used after 24 weeks of pregnancy and in those with fasting blood sugar less than 110 mg/dL (10).

Specific insulins are employed to treat diabetes in pregnant women. The applied dose and regimen are decided by the degree of hyperglycemia. First, women with fasting hyperglycemia may only need a single nocturnal injection of neutral protamine Hagedorn (NPH) insulin at a dosage of 0.2 units/kg while others may merely require prandial insulin to manage post-meal glucose increases. Euglycemia can be sustained with a mixture of NPH-insulin twice daily and a short-acting or rapid-acting insulin analog given immediately before meals if both fasting and post-meal glucose levels are high. In this situation, the per day dosage is usually 0.7-1.0 units/kg, divided evenly between NPH- and prandial-insulin periods (44). Insulin dosages are considered to obtain glycaemic goals while avoiding hypoglycemia. Human insulin (both short-acting and NPH-insulin) and rapid-acting analogs (i.e., lispro and aspart) are all completely risk-free. Long-acting insulin analogs have not really been fully tested in pregnancy (36). In a recent randomized clinical trial by He et al, detemir insulin was found to be comparable to NPH insulin in terms of safety and efficacy (44).

Comparing the oral agents versus insulin treatment in GDM, systematic reviews and meta-analyses of several studies have found that both strategies are equally effective and safe (45, 46). The long-term protection of oral agents in GDM, however, is unknown (46, 47).

Metformin has been shown to achieve comparable glucose regulation to insulin with no difference in

perinatal outcomes (47). When compared to insulin therapy, metformin was reported to be associated with less maternal weight gain while showing a higher risk of preterm birth when used alone. Metformin therapy was also linked to less macrosomia and maternal weight gain in comparison with glyburide (46). Glyburide has been indicated to be as effective as insulin in terms of efficacy and outcomes. During the pregnancy, risk factors contributing to the worsening condition of the mother's blood glucose, along with the urinary tract infections should be considered as well (46).

Moreover, herbal medicine and alternative treatments are widely used among the Iranian populations, probably helping in blood glucose management according to our recently reviewed studies (48, 49) and previous evidence (50). However, precautions are needed for herbal medications during the pregnancy, and an herbal medicine specialist should merely prescribe any of these medications.

Conclusion

Overall, gestational diabetes is associated with an increased risk to both the mother and the fetus during pregnancy and later life. Therefore, these pregnancies require critical care to control blood sugar during pregnancy and reduce perinatal complications. On the other hand, the increasing prevalence of gestational diabetes has caused serious concerns for health systems around the world and its adverse consequences in pregnancy. Accordingly, the latest changes in the guidelines of gestational diabetes should be followed and be taken into account by all healthcare policymakers to be performed in clinics.

Conflict of Interests

None.

Ethical Statement

Not applicable.

Acknowledgment

None.

Authors' Contributions

The study and the search strategy were designed and built by HMM, and then the study was conducted by HMM and SAH. The manuscript was drafted by HMM and its final version was revised by HMM and SAH.

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