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Review

Gestational Diabetes Mellitus

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ABSTRACT

Gestational diabetes mellitus (GDM) refers to the onset of diabetes occurring after the conclusion of the first trimester of pregnancy. GDM is currently one of the most common pregnancy-related medical complications and a cause of diabetes in young women. Maternal overweight and obesity, older age at birth, a history of GDM, a family history of type 2 diabetes mellitus, and ethnicity are important risk factors for GDM development during pregnancy. GDM increases the risk of long-term complications in both the mother and infant, including obesity, impaired glucose metabolism, and cardiovascular disease. It is also associated with adverse pregnancy outcomes such as macrosomia, shoulder dystocia or other birth injuries (also called birth trauma), hypertension, and preeclampsia, perinatal depression, preterm birth, and stillbirth. Managing the mother and infant optimally during long-term follow-up remains challenging. Dietary modification and increased physical activity are the primary treatments for GDM and can alleviate GDM-related complications. However, hypoglycemic agents, traditionally insulin, are used when normoglycemia is not achieved. This review focuses on the current knowledge of GDM and briefly discusses its updates.

Keywords: Gestational diabetes mellitus, risk factors, outcomes, diabetes mellitus, complications

INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as glucose intolerance that occurs in the second or third trimester of pregnancy (1-4). GDM encompasses a range of hyperglycemia, from mild impaired glucose tolerance (IGT) or impaired fasting glucose (IFG) to overt diabetes (5). It is an important risk factor for subsequent type 2 diabetes mellitus (DM) and is typically diagnosed during pregnancy without any symptoms. While GDM usually resolves after childbirth, there is a high risk of recurrence in future pregnancies (3). GDM poses various risks to the mother, fetus, and newborn, with potential long-term consequences such as obesity, glucose intolerance, and diabetes in childhood and adulthood (6). Screening, diagnosis, and effective treatment of GDM can improve maternal and perinatal outcomes and prevent future diabetes in both the mother and child (7).

The prevalence of GDM indirectly reflects the future prevalence of type 2 diabetes in a given population (1). The exact prevalence of GDM is unknown and can vary based on screening and diagnostic criteria, population region, data collection methods, and sample selection (8,9). Generally, the prevalence of GDM ranges from 2% to 6%, but certain studies have reported rates as high as 10% to 20% (10-13). In the Turkish population, it is estimated that the incidence of GDM falls between 4% and 10% (3). In a study conducted with a two-step diagnostic method involving 2,643 pregnant women from 51 centers across different regions, the prevalence of GDM in the Turkish population was found to be 16.2%, with no significant difference between urban and rural areas (9). GDM accounts for approximately 90% of diabetic pregnancies (14). In recent years, the increasing rates of advanced maternal age and obesity have contributed to the rising prevalence of GDM. According to the TURDEP II study, the prevalence of DM in Turkey was reported as 16.5% (15).

For women at risk of developing GDM, it is important to assess GDM or gestational glucose intolerance during the initial prenatal visit, with tests interpreted as if the woman were not pregnant (3,16). The American Diabetes Association (ADA) has outlined low and high-risk factors for GDM development, as shown in **Table 1** (3,5,7,16). Pre-conceptional overweight or obesity are major risk factors for GDM (5). Maternal age has a strong correlation with GDM. Although factors such as

Table 1. Risk assessment in pregnant for GDM development

Low-risk	High-risk	
Age <25 Normal weight before pregnancy An ethnic group with a low prevalence of DM No diabetes in first-degree relatives No history of abnormal glucose tolerance No history of poor obstetric outcome	Overweight or obesity (BMI ≥25kg/m2) Advanced age (>40) Ethnicity Family history of type 2 DM Previous history of prediabetes Previous history of GDM Presence of glycosuria Parity (more than 20 weeks of pregnancies) Multiple pregnancies Genetic factors Polycystic ovary syndrome Cigarette smoking	Pre-pregnancy diet (rich in red/processed meat products) Physical inactivity Short individuals α-Thalassemia Hypertension Hyperlipidemia Corticosteroids or antipsychotic medication Macrosomia (birth ≥4.5kg) Low birth weight History of poor obstetric outcome Acanthosis nigricans Male fetus

DM; diabetes mellitus

body mass index (BMI), previous history of GDM, and family history of diabetes are independent predictors for GDM development, GDM can still occur in 1 out of 20 low-risk pregnancies (9).

PATHOPHYSIOLOGY of GESTATIONAL DIABETES

GDM is a heterogeneous disease resulting from the interaction between genetic and environmental risk factors. In addition to diet and lifestyle factors, environmental and psychosocial factors are thought to be possible contributors to the risk of developing GDM (5).

In fact, it has been known for a long time that insulin resistance develops similarly to type 2 DM during pregnancy (17). Increased insulin resistance and pancreatic β-cell dysfunction constitute the main physiopathological mechanism in women with GDM (2,5,6,8,18). Insulin resistance during pregnancy occurs at varying rates. It may be the result of maternal obesity with adipocytokine production or increased diabetogenic placental hormone production (2,8,19). As insulin resistance increases during pregnancy, there is a compensatory increase in insulin secretion to induce euglycemia (1,2,5).

Pancreatic β-cell hyperplasia occurs in response to glycogenic hormones during pregnancy (PAPP-A; pregnancy-associated plasma protein A, PLGF; placental growth factor, SHBG; sex hormone binding globülin, etc.) (19). Physiological resistance to the effect of insulin becomes evident in the second trimester and insulin sensitivity gradually decreases (2,17). Impairment of glucose tolerance occurs especially in the third trimester. β-cell dysfunction often precedes pregnancy and is

Table 2. Biomarkers result in GDM and their mechanism of action was summarized

Biomarkers	Mechanism of action	Probable pathway in GDM
Adiponectin	Modulation of glucose and lipid metabolism. Involvement in inflammation, apoptosis, and angiogenesis.	Low levels associated with decreased insulin sensitivity and GDM
Leptin	Adjustment of energy balance and expenditure. Act on hormone regulation and immunity.	Increased leptin causes hyperinsulinemia and insulin resistance
PAPP-A	Increase the bioavailability of IGF-1 and promotes somatic growth. Role in wound healing and bone remodeling.	Decreased levels of PAPP-A contribute to an increase in insulin resistance
PLGF	Vascular endothelial growth factor-like protein. Role in angiogenesis and placentation.	High PLGF levels promote the abnormal vascular network in the placenta of GDM pregnancies
TNF-α	The regulation of immune cells, inflammation, and autoimmune diseases.	Increased levels of TNF-α impair insulin signaling and beta-cell function, leading to insulin resistance and GDM
CRP	Role in tissue injury, inflammation, and infection	High levels associated with insulin resistance and systemic inflammation
IL-6	Role in immune response regulation, inflammation, and hematopoiesis.	Increased secretion by adipocytes and placental cells, leading to a chronic inflammatory process and insulin resistance
SHBG	Glycoprotein that binds androgen and estrogen.	Decrease SHBG levels associated with hyperinsulinemia and GDM

GDM; gestational diabetes mellitus, PAPP-A; pregnancy-associated plasma protein A, IGF-1; insulin growth factor 1, PLGF; placental growth factor, TNF-α; tumor necrosis factor α, CRP–C; reactive protein, IL-6; interleukin 6, and SHBG; sex hormone-binding globulin. (Retrieved from reference 20)

clinically manifested by increased insulin resistance during pregnancy (5). The rapid decrease in insulin resistance after birth suggests that placental hormones play a major role in insulin resistance (2). There are numerous biomarkers have been described in GDM (Table 2) (20).

Basal endogenous glucose production, especially hepatic glucose production, is 30% higher in pregnant women with GDM compared to healthy pregnant women. Peripheral insulin sensitivity decreases by approximately 50% in late pregnancy. In late pregnancy, the skeletal muscle content of insulin receptor substrate 1 (IRS1), one of the signal molecules, is lower in pregnant women with GDM compared to non-pregnant women. Additionally, the autophosphorylation of the insulin receptor β-subunit (IRβ) is lower in women with GDM compared to pregnant women with normal glucose tolerance. Maternal amino acid and lipid metabolism are also affected by decreased insulin sensitivity during pregnancy, which is associated with increased fetal growth and adiposity (5). Glucose transfer across the placenta stimulates fetal insulin secretion, and insulin acts as an essential growth hormone (17). Fetal insulin stimulates triglyceride synthesis, leading to increased white adipose tissue in the fetus (5).

Current evidence suggests that pancreatic β-cell defects in GDM result from similar underlying causes of hyperglycemia in general, including autoimmune disease, monogenic causes, and insulin resistance (2). Although genetic inheritance is believed to play a role in the etiology of GDM, studies examining the relationship between specific genetic factors and GDM are limited. Only a small proportion (2-13%) of women with GDM have antibodies against specific β-cells. Approximately 5% of women with GDM also have monogenic diabetes variants that involve a glucokinase mutation, which is most commonly observed in Caucasians (5,12). As a result, 5% of cases may exhibit maturity-onset diabetes of the young (MODY), and 2% may have type 1 diabetes mellitus (DM).

DIAGNOSTIC AND SCREENING CRITERIA FOR GESTATIONAL DIABETES

According to standard diagnostic criteria, it is recommended to screen pregnant women with risk factors for the development of DM for undiagnosed prediabetes and diabetes during their initial prenatal visit (6). Early screening for GDM is particularly important for women in populations with a high prevalence of type 2 DM (8).

During the first prenatal visit, fasting plasma glucose (FPG), HbA1C, or random plasma glucose (PG) should be measured in all pregnant women or those at high risk (20). Selective screening for GDM may result in a missed diagnosis in over 40% of GDM cases. If the FPG falls within the prediabetic range (100-125 mg/dl) at the beginning of pregnancy, it should be interpreted as in non-pregnant women, preferably by conducting an oral glucose tolerance test (OGTT) or assessing HbA1c. Conversely, if the 2nd-hour PG in the OGTT is between 140-199 mg/dl (or HbA1c is between 5.7-6.4%), pregestational prediabetes should be considered, and the pregnant woman should be monitored as if she has diabetes. A fasting plasma glucose level of ≥126 mg/dL (≥7.0 mmol/l), random plasma glucose level of ≥200 mg/dL (≥11.1 mmol/l), or HbA1C level of ≥6.5%, confirmed by the same or a subsequent test, indicates overt diabetes (3,20). If the 2nd-hour PG in the OGTT is ≥200 mg/dL (or HbA1C is ≥6.5%), the diagnosis of "pregestational diabetes" is made (3). All women without diabetes who have normal test values at the beginning of pregnancy should be screened again between 24 and 28 weeks of pregnancy (1,6,13).

Screening for GDM between 24 and 28 weeks of pregnancy: The International Association of Diabetes and Pregnancy Working Groups (IADPSG) recommends a 75g OGTT for screening during this period (20). Some guidelines also recommend a single-step 75g OGTT using IADPSG criteria during gestational weeks 24-28 (21,22). A one-step approach may be preferred if the prevalence of GDM is high (16). It is believed that the rate of GDM diagnosis may be lower with a two-step approach compared to a single-step approach (17). It is estimated that approximately 25% of GDM cases could be missed with the two-step method (5).

There is no consensus regarding the use of diagnostic tests and glucose threshold values for GDM (3,7). As the adoption of the one-step diagnostic approach increases, evidence suggests that perinatal outcomes are favorable and there is actually a "cost-effective" improvement in pregnancy outcomes. However, the one-step approach may simplify the diagnosis of GDM and increase the number of pregnant women diagnosed with GDM, leading to potential economic and emotional challenges (3,7,8). While national guidelines in Turkey suggest either approach, most centers still prefer the two-step approach using the Carpenter-Coustan criteria (9).

GDM diagnosis can be made with one of two approaches (Table 3).

1. "One step" approach with 75 g OGTT according to the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) criteria; OGTT is performed in the morning after at least 8 hours of night fasting. If any value of serum glucose exceeds the threshold, GDM is diagnosed (21).

2. Scanning by using 50 g of glucose followed by 100

g of glucose "two-step" approach (Carpenter-Coustan criteria) (24)

Table 3. Glucose threshold values of OGTT in the diagnosis of GDM

	One Step- 75 gr glucose	'Two Steps- 100 gr glucose
FPG	92 mg/dL (5.1 mmol/L)	95 mg/dL (5.3 mmol/L)
1 hour	180 mg/dL (10.0 mmol/L)	180 mg/dL (10.0 mmol/L)
2 hours	153 mg/dL (8.5 mmol/L)	155 mg/dL (8.6 mmol/L)
3 hours		140 mg/dl (7.8 mmol/L)

FPG; fasting glucose

Women who do have not pregestational DM should be screened by random plasma glucose following 50 g glucose ingestion within 24-28 weeks of pregnancy (fasting is not necessary). If the 1st hour PG ≥140 mg/dl a 100 g OGTT is performed in the morning after 8 hours of night fasting. GDM is diagnosed when at least two criteria are met or exceeded (6).

In a 50 g glucose loading test when 1st-hour glucose is ≥140 mg/dl (7.8 mmol/L), it is recommended to perform 100 g OGTT (6). With this approach, ~80% of women with GDM are identified, and when the threshold value is set to ≥130 mg/dL (7.2 mmol/L) sensitivity increases to ~90% (1,14,15). It is recommended that those with PG ≥180 mg/dl in the 1st hour should be considered as GDM without the need for OGTT and follow-up and treatment should be started. Those who pass only one cut-off point in the 100-gr OGTT test are considered 'Gestational Glucose Intolerance' and it is recommended that these pregnant women be followed closely like GDM (3).

In the single-step approach, when one or more glucose values exceed the threshold, the incidence of preeclampsia was doubled, and the incidence of preterm birth and primary cesarean section was 45% higher. It has been reported that high FPG levels (lower than the diagnosis of diabetes) in the first trimester are associated with a later diagnosis of GDM and risks of adverse pregnancy outcomes (20). The diagnosis of GDM is not possible with the OGTT after surgical procedures that affect absorption (dumping syndrome) (25).

HbA1c values are useful in the evaluation of pregestational diabetes; however, when normal, it is not useful for the management of GDM (1). HbA1C is slightly lower in pregnancy than in non-pregnant women with increased erythrocyte cell turnover (26). HbA1C was ≥5.9% in early pregnancy is associated with poor outcomes such as congenital malformation risk, preeclampsia, shoulder dystocia and perinatal death (27).

TREATMENT of GDM

In women with a history of GDM, the development of type 2 DM can be prevented or delayed by lifestyle modification and/or medical treatment (11,28). The incidence of hypertension and preeclampsia also decreases with GDM treatment (3). The main goal of GDM treatment is to prevent fetal overgrowth and pregnancy complications (5,24). If left untreated, perinatal morbidity and mortality may increase (17).

In the prenatal period, treatment of women with a history of GDM should consist of medical nutrition therapy (MNT) and weight management, exercise, blood glucose self-monitoring (SMBG), and pharmacological therapy if necessary (8). All pregnant women with GDM should be taught to measure blood glucose at home (3). They are encouraged to monitor their own blood sugar levels before main meals and 1-2 hours after meals. Diet modification and increased physical activity are first-line treatments for GDM; however, insulin is usually used when normoglycemia cannot be achieved with this approach (5).

Lifestyle Change

Mild GDM can be treated 80-90% with only lifestyle changes (5,6.10,26). It has been shown that the risk of GDM can be reduced by diet, exercise, and lifestyle changes, especially when it is initiated in the first or second trimester of pregnancy (26). In high-risk women, it is recommended to start to lifestyle modification in early pregnancy and continue throughout pregnancy. A moderately personalized lifestyle change reduced the incidence of GDM in high-risk pregnant women by 39%. Findings in lifestyle intervention studies that focused on preventing type 2 diabetes were also encouraging, showing a risk reduction of 58% (18). It shows that it can be prevented by maintaining (BMI) of < 25 kg/m2, exercising ≥ 30 minutes a day, and not smoking (5).

Following the diagnosis of GDM, treatment begins with medical nutrition therapy, physical activity, and weight management depending on pregestational weight (26). Expected weight gain in normal pregnancy varies with pre-pregnancy weight. Recommended weight gain rates during pregnancy are shown in **Table 4** (13,25).

Table 4. Recommended weight gain rates during pregnancy

BMI, kg/m^2	Total weight gain	2. ve 3. trimester weekly weight gain
≤18,5 kg/m2	12.5–18 kg	0.5–0.6 kg
18.5–24,9 kg/m2	11.5–16 kg	0.4–0.5 kg
25.0–29,9 kg/m2	7–11.5 kg	0.2–0.3 kg
≥30 kg/m2	5–9 kg	0.2-0.3 kg

BMI; body mass index

Exercise

Regular physical exercise, fitness programs, or sports reduce the risk of GDM and increase the capacity to cope with pregnancy and childbirth, especially in women

who had pregestational obesity. Short exercise programs are beneficial in the first hour after main meals (25). The simple unaided physical exercise should be brisk walking for at least 30 minutes, at least 3 times a week. Physical activity should begin before conception or in the first trimester (1,25). The optimal type of exercise is unknown, but walking is generally recommended (10). Moderate-intensity aerobic activity (walking, cycling, or swimming) helps control blood sugar (13). Exercise helps to control both fasting and postprandial glucose levels by increasing insulin sensitivity (8,10).

Medical Nutrition Therapy

Medical nutrition therapy is defined as "designing meals with controlled carbohydrate levels for normal nutrition, normal sugar levels, and prevention of ketosis and adequate nutrition" (10). A food plan is designed to improve fetal/neonatal and maternal health, achieve glycemic goals, and promote appropriate gestational weight gain should ensure adequate caloric intake (26). During pregnancy, diets with high fat and low fiber intake and high glycemic index increase the risk of developing GDM; therefore, it is thought that a low glycemic index and high fiber diet greatly reduces the need for insulin in diabetic patients (10).

Pregnant should be counseled by a dietitian following diagnosis of GDM to initiate MNT, which forms the basis of any management plan, and should be advised to eat a main meal and 3 snacks (8). The nutrition program should be prepared in accordance with the targeted weight and physical capacity of the pregnant woman, as well as taking into account the needs of the fetus; targeted normoglycemia should be regulated so that ketosis does not occur (1,13). Maternal ketonemia and/or ketonuria in pregnant women with diabetes have been associated with lower mental and/or motor function in offspring (5).

Recommended food content; carbohydrates should be 40-55%, protein 20%, fat 25-40%. The percentage of carbohydrates should not be less than 40% or 175 g/day. Carbohydrates with high fiber content (28 g fiber) and low glycemic index should be preferred, and at least 71 g protein should be taken (10,24,25). The number of carbohydrates should be lower at breakfast than at lunch and dinner (25).

There is no conclusive research that specifically defines optimal caloric intake for women with GDM or suggests that their caloric needs differ from pregnant women without diabetes (26). Calorie intake is calculated based on ideal body weight [25-35 kcal/kg/day (ideal weight)] (1). It is 30 kcal/kg/day for women with normal body mass index and 24 kcal/kg/day for overweight women. However, 12-15 kcal/kg/day can be recommended for obese pregnant. Average calorie restriction (33% reduction in calorie intake) does not lead to ketosis but controls weight gain and glucose levels in obese women (10). This calorie content will ensure that 75-80% of pregnant women are normoglycemic (1). Most pregnant should receive 350 calories more from the beginning of the 4th month of pregnancy (13).

Pharmacological Treatment

Pharmacological therapy should be initiated when hyperglycemia persists after a fortnight of lifestyle change (5,8). Ultrasonography-based assessment of fetal growth can also help adjust the intensity of glucose control needed. If the baby is growing appropriately, especially with fetal abdominal circumference <75 percentile, it may be safe to delay the initiation of pharmacological therapy. Conversely, excessive fetal growth may lead to the intensification of therapy to achieve low glycemic targets (5).

Oral Antidiabetics (OAD): OAD is not recommended during pregnancy. OAD has no long-term safety data (8,25). Insulin therapy should be initiated in women with type 2 DM who become pregnant unplanned (3). Metformin and glyburide (glibenclamide) are not recommended as first-line therapy because they cross the placenta and are lacking in fetal safety data (26).

Metformin may slightly increase the risk of prematurity (26). Metformin crosses the placenta but is not associated with teratogenesis (3). The most important advantage is that it does not cause hypoglycemia. There is increasing concern about the safety of glyburide in GDM (1). Following the widespread use of glyburide in the USA, it has been observed that there is a risk of large infants according to gestational age (LGA), neonatal hypoglycemia, birth injury, and respiratory distress in infants of treated women (1,5).

Insulin: Traditionally, insulin should be started if glycemic therapy goals are not achieved within one to two weeks with lifestyle changes (5). Since insulin does not measurably cross the placenta, it is preferred and recommended first-line agent in treatment (26). It should be arranged according to the SMBG and ketone monitoring to be performed by the patient (3). Although insulin is usually started when glycemic targets are exceeded, some studies suggest that insulin should be initiated solely on the basis of fetal ultrasonographic parameters such as increased fetal abdominal circumference (8).

Both multiple daily insulin injections and continuous subcutaneous insulin infusion are reasonable administration strategies and neither has been shown to be superior to the other during pregnancy. Insulin requirement typically rises during the early stages of the first trimester of pregnancy, but gradually decreases within the span of 9-16 weeks. Repeated and rapidly

increasing insulin resistance after 16 weeks requires an approximately 5% weekly increase in insulin dose to achieve glycemic targets. By the end of the third trimester, the insulin requirement roughly doubles (26).

Types of insulin that can be used during pregnancy include intermediate-acting insulin (neutral protamine Hagedorn-NPH), long-acting insulin (detemir), and rapid-acting insulin analogs (lispro and aspart). It has been shown that the safety and efficacy of insulin detemir are not inferior to NPH insülin (1,5,8). Insulin detemir has been associated with less hyperglycemia and hypoglycemia than NPH insulin. Although data in regard to insulin glargine use is not sufficient yet, published cohort studies have not raised concerns about its use in pregnancy (5). Hypoglycemia is a risk factor and can develop with aggressive management of glucose levels with insulin. Patients and family members should be informed about the monitoring and treatment of hypoglycemia (1).

The total insulin dose varies between 0.7-2 IU/kg (1). In general, a smaller proportion (<50%) of the total daily dose should be given as basal insulin and a larger proportion (>50%) as postprandial insulin. Intermediate/long-acting insulin (NPH/detemir) once or twice daily or multiple-dose insulin therapy (a basal-bolus regimen using rapid-acting insulin before main meals) may be preferred (3,5).

Insulin can be discontinued immediately after birth; however, glucose monitoring should be performed for several days to exclude ongoing hyperglycemia (5).

GLYCEMIC CONTROL GOALS in PREGNANCY

Ideally, the HbA1C target in pregnancy is 6% if achievable without significant hypoglycemia; however, the target can be stretched up to 7% to prevent hypoglycemia. In the second and third trimesters, the risk of large-growth baby development, preterm birth, and preeclampsia is lowest, with a target of HbA1C ≤ 6% (26) (Table 5).

Table 5. Glycemic targets in pregnants

FPG	<95 mg/dL (5.3 mmol/L)
Postprandial 1-hour	<140 mg/dL (7.8 mmol/L)
Postprandial 2-hour	<120 mg/dL (6.7 mmol/L)
HbA1C	6-6.5% (42-48 mmol/mol)

FPG; FPG; fasting glucose

MATERNAL and FETAL COMPLICATIONS in GDM

It is thought that there is a relationship between adverse pregnancy outcomes, even at maternal mildly elevated glucose levels (5,8,11,25). Short- and long-term complications for the mother and fetus are shown in Table 6 (8,16,22,25,26).

Table 6. Maternal/fetal short- and long-term complications in GDM

Maternal Complications	Fetal Complications
Hypertensive disorders Preterm birth Cesarean delivery Shoulder dystocia Preeclampsia Polyhydramnios Birth canal lacerations Metabolic comorbidities (diabetes, metabolic syndrome, cardiovascular diseases)	Neonatal hypoglycemia Hyperbilirubinemia Macrosomia Polycythemia Neonatal hypocalcemia, hypomagnesemia Respiratory distress syndrome Metabolic comorbidities (obesity, diabetes, prediabetes, hypertension, metabolic syndrome) fetal death

In the Hyperglycemia and Adverse Outcomes in Pregnancy (HAPO) study, a multicenter, multinational study, 75-g 2-hour OGTT was administered to 23,316 pregnants on 24-28s of pregnancy week (average 28 weeks) and a relationship between maternal glucose, newborn adiposity, and increased fetal insulin has been demonstrated (29). Shoulder dystocia in GDM increases the risk of perinatal death and birth trauma and makes the need for cesarean section more likely. Insulin-sensitive tissue, such as adipose tissue around the chest, shoulders, and abdomen, especially in the fetus, is overgrowth (17).

GDM carries a high risk for pyelonephritis, asymptomatic bacteriuria, and preeclampsia and has a 10% risk of polyhydramnios. Fetal risks of poor glucose control include stillbirths and macrosomia. Since glucose intolerance develops in the later stages of pregnancy, there is no increased risk for congenital anomalies (1). Hyperglycemia in pregnancy, whether associated with high birth weight or not, is associated with obesity and glucose intolerance that develops in these infants later in life (29).

There is no common consensus on the time and mode of delivery in pregnant with GDM; however, when the estimated birth weight is ≥4.5 kg, the risk of shoulder dystocia is usually significantly increased and cesarean delivery is recommended for those (25).

POSTNATAL MANAGEMENT in GDM

In GDM, insulin resistance decreases rapidly, usually within six weeks after birth, and glucose tolerance returns to normal in approximately 95% of cases (1,17). In postnatal 4-12. weeks women with GDM should be screened for prediabetes or diabetes diagnoses according to standard criteria by performing 75 g OGTT. Those women should also be screened at least every 3

years for the development of diabetes or prediabetes (3,6,26). Intensive lifestyle changes and/or metformin are recommended for women found to be prediabetic to prevent or delay diabetes (3,6,8). While the risk of progression to diabetes decreased by 35% in these women after a follow-up period of about 10 years; when metformin is added to lifestyle changes, the risk of developing DM is reduced by 40-50% (3,5). However, since metformin passes into milk during lactation, the use of metformin is not preferred except for limited indications.

There is a 7-8 times increased risk of type 2 DM development in women following GDM (11,25,27). The risk of new-onset type 2 DM increases linearly by 9.6% with each year of follow-up in those women (30). The risk of developing DM in women is 35-60% within 10 years and 50-70% after 15-20 years (11,25-27). Even in the first year after conception, approximately 20% of European women have various forms of impaired glucose metabolism. Impaired glucose tolerance does not improve after pregnancy in approximately 13-40% of cases (25).

The risk of conversion to overt diabetes is increased in women who are obese before conception, Asian women, diagnosed with GDM before 24 weeks, receiving insulin therapy, OGTT ≥200 mg/dl at the 1st hour of pregnancy, and HbA1C ≥5.7% at the diagnosis of GDM (25). Weight gain during pregnancy or postpartum is associated with an increased risk of adverse pregnancy outcomes in subsequent pregnancies and earlier progression to type 2 DM (25). FPG levels during pregnancy are also thought to be an important predictor of conversion to postpartum DM (8). The incidence of type 1 DM in risk groups 5-10 years after GDM is 2,3-10% (25).

The recurrence rate of GDM depends on the following factors; (10,12,25)

- Parity,
- BMI (>30 kg/m2),
- Early diagnosis of GDM (<24 weeks),
- Insulin requirement,
- Weight gain of more than 3 kg between pregnancies,
- the interval between pregnancies (<24 months),
- In ethnic groups at high risk of diabetes (Asia, Latin America), the risk rises to 50-84% with a high FPG two months after birth.

In different studies, it has been observed that the disease occurs at a rate of 30-70% in subsequent pregnancies (10).

Epidemiological studies show that maintaining physical activity, adopting healthy dietary patterns, avoiding post-pregnancy weight gain, and frequent, prolonged and more intense breastfeeding reduce the risk of overt progression to diabetes. Breastfeeding improves weight and glucose tolerance, so it should be encouraged (8).

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REFERENCES

1.Masharani U, German MS. *Pancreatic hormones and diabetes mellitus. In: Greenspan's basic & clinical endocrinology.* Gardner DG, Shoback D (eds). 10th ed. San Francisco (SF): McGraw-Hill education; c2018:677-682.
2.Buchanan TA, Xiang A, Kjos SL, Watanabe R. What is gestational diabetes? [published correction appears in Diabetes Care. 2007 Dec;30(12):3154]. *Diabetes Care*. 2007;30 Suppl 2:S105-S111. doi:10.2337/dc07-s201
3.TEMD; Diabetes Mellitus Çalışma ve Eğitim Grubu. *Diabetes mellitus ve komplikasyonlarının tanı, tedavi ve izlem kılavuzu-2019* 12. baskı. Ankara: Miki Matbaacılık San. ve Tic. Ltd. Şti; c2019.
4.Vounzoulaki E, Khunti K, Abner SC, Tan BK, Davies MJ, Gillies CL. Progression to type 2 diabetes in women with a known history of gestational diabetes: systematic review and meta-analysis. *BMJ*. 2020;369:m1361. Published 2020 May 13. doi:10.1136/bmj.m1361
5.McIntyre HD, Catalano P, Zhang C, Desoye G, Mathiesen ER, Damm P. Gestational diabetes mellitus. *Nat Rev Dis Primers*. 2019;5(1):47. Published 2019 Jul 11. doi:10.1038/s41572-019-0098-8
6.Amer American Diabetes Association. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2020. *Diabetes Care*. 2020;43(Suppl 1):S14-S31. doi:10.2337/dc20-S002
7.Rani PR, Begum J. Screening and Diagnosis of Gestational Diabetes Mellitus, Where Do We Stand. *J Clin Diagn Res*. 2016;10(4):QE01-QE4. doi:10.7860/JCDR/2016/17588.7689
8.Mirghani Dirar A, Doupis J. Gestational diabetes from A to Z. *World J Diabetes*. 2017;8(12):489-511. doi:10.4239/wjd.v8.i12.489
9.Aydın H, Çelik Ö, Yazıcı D, et al. Prevalence and predictors of gestational diabetes mellitus: a nationwide multicentre prospective study. *Diabet Med*. 2019;36(2):221-227. doi:10.1111/dme.138577.
10.Dolatkhah N, Hajifaraji M, Shakouri SK. Nutrition Therapy in Managing Pregnant Women With Gestational Diabetes Mellitus: A Literature Review. *J Family Reprod Health*. 2018;12(2):57-72.
11.Damm P, Houshmand-Oeregaard A, Kelstrup L, Lauenborg J, Mathiesen ER, Clausen TD. Gestational diabetes mellitus and long-term consequences for mother and offspring: a view from Denmark. *Diabetologia*. 2016;59(7):1396-1399. doi:10.1007/s00125-016-3985-5
12.Ben-Haroush A, Yogev Y, Hod M. Epidemiology of gestational diabetes mellitus and its association with Type 2 diabetes. *Diabet Med*. 2004;21(2):103-113. doi:10.1046/j.1464-5491.2003.00985.
13.International Diabetes Federation. Management of gestational diabetes mellitus in the community, Training manual for community health workers; 2015: 1-19.
14.American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2009;32 Suppl 1(Suppl 1):S62-S67. doi:10.2337/dc09-S062
15.Satman I, Omer B, Tutuncu Y, et al. Twelve-year trends in the prevalence and risk factors of diabetes and prediabetes in Turkish adults. *Eur J Epidemiol*. 2013;28(2):169-180. doi:10.1007/s10654-013-9771-5
16.American Diabetes Association. Standards of medical care in diabetes--2010 [published correction appears in Diabetes Care. 2010 Mar;33(3):692]. *Diabetes Care*. 2010;33 Suppl 1(Suppl 1):S11-S61. doi:10.2337/dc10-S011
17.Farrar D, Duley L, Dowswell T, Lawlor DA. Different strategies for diagnosing gestational diabetes to improve maternal and infant health. *Cochrane Database Syst Rev*. 2017;8(8):CD007122. Published 2017 Aug 23. doi:10.1002/14651858.CD007122.pub4
18.Koivusalo SB, Rönö K, Klemetti MM, et al. Gestational Diabetes Mellitus Can Be Prevented by Lifestyle Intervention: The Finnish Gestational Diabetes Prevention Study (RADIEL): A Randomized Controlled Trial [published correction appears in Diabetes Care. 2017 Jun 14;:]. *Diabetes Care*. 2016;39(1):24-30. doi:10.2337/dc15-0511
19.Prutsky GJ, Domecq JP, Sundaresh V, et al. Screening for gestational diabetes: a systematic review and meta-analysis. *J Clin Endocrinol Metab*. 2013;98(11):4311-4318. doi:10.1210/jc.2013-2460
20.International Association of Diabetes and Pregnancy Study Groups Consensus Panel, Metzger BE, Gabbe SG, et al. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care*. 2010;33(3):676-682. doi:10.2337/dc09-1848

21.Naeh A, Maor-Sagie E, Hallak M, Gabbay-Benziv R. Early Identification of the Maternal, Placental and Fetal Dialog in Gestational Diabetes and Its Prevention. *Reproductive Medicine*. 2022; 3(1):1-14. https://doi.org/10.3390/reprodmed3010001
22.Zhu Y, Zhang C. Prevalence of Gestational Diabetes and Risk of Progression to Type 2 Diabetes: a Global Perspective. *Curr Diab Rep*. 2016;16(1):7. doi:10.1007/s11892-015-0699-x
23.Li-Zhen L, Yun X, Xiao-Dong Z, et al. Evaluation of guidelines on the screening and diagnosis of gestational diabetes mellitus: systematic review. *BMJ Open*. 2019;9(5):e023014. Published 2019 May 5. doi:10.1136/bmjopen-2018-023014.
24.Carpenter MW, Coustan DR. Criteria for screening tests for gestational diabetes. *Am J Obstet Gynecol*. 1982;144(7):768-773. doi:10.1016/0002-9378(82)90349-023.
25.Schäfer-Graf UM, Gembruch U, Kainer F, et al. Gestational Diabetes Mellitus (GDM) - Diagnosis, Treatment and Follow-Up. Guideline of the DDG and DGGG (S3 Level, AWMF Registry Number 057/008, February 2018). *Geburtshilfe Frauenheilkd*. 2018;78(12):1219-1231. doi:10.1055/a-0659-2596
26.American Diabetes Association. 14. Management of Diabetes in Pregnancy: *Standards of Medical Care in Diabetes-2019*. *Diabetes Care*. 2019;42(Suppl 1):S165-S172. doi:10.2337/dc19-S014
27.Brown FM, Wyckoff J. Application of One-Step IADPSG Versus Two-Step Diagnostic Criteria for Gestational Diabetes in the Real World: Impact on Health Services, Clinical Care, and Outcomes. *Curr Diab Rep*. 2017;17(10):85. Published 2017 Aug 10. doi:10.1007/s11892-017-0922-z26.
28.Gilinsky AS, Kirk AF, Hughes AR, Lindsay RS. Lifestyle interventions for type 2 diabetes prevention in women with prior gestational diabetes: A systematic review and meta-analysis of behavioural, anthropometric and metabolic outcomes. *Prev Med Rep*. 2015;2:448-461. Published 2015 May 24. doi:10.1016/j.pmedr.2015.05.009
29.HAPO Study Cooperative Research Group. Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study: associations with neonatal anthropometrics. *Diabetes*. 2009;58(2):453-459. doi:10.2337/db08-1112.
30.Li Z, Cheng Y, Wang D, et al. Incidence Rate of Type 2 Diabetes Mellitus after Gestational Diabetes Mellitus: A Systematic Review and Meta-Analysis of 170,139 Women. *J Diabetes Res*. 2020;2020:3076463. Published 2020 Apr 27. doi:10.1155/2020/3076463