Current approaches in gestational diabetes mellitus

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ABSTRACT

Gestational diabetes mellitus (GDM) is one of the most common medical complications in pregnancy and has become a global public health issue in terms of causing fetal and maternal morbidity and mortality in short- and long-term. The number of cases of GDM all over the world has been increasing day by day and they include risks for mother and baby health compared to healthy pregnancies. GDM screening and diagnostic phase has complete different approaches and there is no common consensus. Once GDM is diagnosed, pharmacologic treatment can be necessary in addition to strict blood sugar follow-up, regular exercise, and diet regulation. In postpartum period, medical monitoring is also necessary due to increased risk of diabetes mellitus in women with GDM. In this paper, we will also discuss approaches suggested in the GDM in the context of current guidelines and literature.

Keywords: Hyperglycemia, pregnancy, gestational diabetes mellitus, current approaches

Gestational diabetes mellitus (GDM) is the most common complication of pregnancy and is defined as glucose intolerance at various grades beginning in pregnancy in women with carbohydrate intolerance or diagnosed for the first time during pregnancy [1]. The incidence of GDM has been increasing worldwide with the effect of factors such as increased obesity rates and advanced maternal age [2]. The prevalence of GDM varies widely depending on the population and diagnostic criteria. The global prevalence of GDM varies from 1% to 28%, depending on population characteristics (maternal age, socioeconomic status, race, body composition, etc.), screening methods and diagnostic criteria [3]. In a limited number of studies conducted in different regions of Turkey, it was reported that the prevalence of GDM varied between 3% and 9.2%, and this ratio increased up to 11.4% depending on the diagnostic criteria used [4-6].

Pathophysiology

In the formation of gestational diabetes, the main problem is a decrease in maternal insulin sensitivity [7]. In normal pregnancy, fasting blood sugar and HbA1c levels are lower than those of non-pregnant women due to peripheral use of glucose, increased glycogen storage in tissues and increased fetal glucose utilization. A decrease in maternal HbA1c and fasting blood sugar are caused by the supply of glucose into fetus with active transport through facilitated diffusion and trophoblasts via glucose transporter-1 (GLUT-1), in other words, are caused by the diffusion of glucose over a wider area [8]. During pregnancy, a progressive insulin resistance occurs due to the effects of diabetogenic hormones secreted from the placenta (growth hormone, corticotropin-releasing hormone [CRH], placental lactogen, progesterone), maternal postprandial blood glucose level is elevated, and this

process leads to fetal glucose transport [9]. The formation of maternal insulin resistance is also influenced by agents that decrease insulin sensitivity such as tumor necrosis factor alpha (TNF-α), leptin, adiponectin, and resistin [10]. In a recent study, it was reported that Interleukin-6 (IL-6), an inflammatory marker, could be used as a predictor of GDM development regardless of adipose tissue, especially in the first 3 months [11]. Insulin secretion increases especially in the first trimester of pregnancy depending on the change in insulin sensitivity during this physiological adaptation during pregnancy. This increase in insulin secretion is crucial for cellular proliferation, tissue development and differentiation. If increased insulin requirement cannot be met in the long-term, GDM develops due to impaired beta-cell function [12].

Genetic Factors Associated with GDM

The increased risk of type 2 diabetes mellitus (DM) in patients with GDM in the later stages of life suggests that this disease is a polygenic, heterogeneous disease similar to type 2 DM. Genetic studies suggested that some genes associated with insulin secretion, insulin and insulin receptors, GDM and play a role in the pathogenesis of GDM, especially mutations in KCNJ11 and ABCC8 genes, which causes impairment of insulin secretion [13].

Fetal and Maternal Consequences of GDM

Many studies in the literature indicate that increased maternal glucose levels have negative consequences for both mother and fetus. As noted in the Hyperglycemia and Adverse Pregnancy Outcome study (HAPO), increased maternal blood glucose level can cause multiple complications for both fetus and mother, independent of factors such as body mass index (BMI) and weight gain [14]. If gestational beta-cell compensation secondary to decreased insulin sensitivity is not achieved in the long term, it causes beta-cell insufficiency and loss of function, resulting in progression of hyperglycaemia and DM. The fact that the women developed GDM have intolerance to high levels of insulin secretion for a long time, is associated with mild inflammation such as obesity, and decreased adiponectin released from adipose tissue, and the addition of factors related to individual sus-

ceptibility to this condition. Type 2 DM occurs as a result of long-term destruction of beta-cells and loss of function. In addition, pregnancy causes a threefold increase in the risk of developing DM following GDM and a prolonged period with insulin resistance, independent of the well-known effects of weight gain [15-17]. It was reported that the prevalence of hypertension development secondary to hyperinsulinemia associated with weight gain and sodium retention in women with GDM has been increased [18]. In the HAPO study, women with GDM with a high body mass index were reported to have a significantly higher risk of developing preeclampsia than women with GDM with a low body mass index [14]. It was shown that the risk of preeclampsia in women with GDM due to the presence of adverse factors such as impaired angiogenesis, endothelial damage, oxidative stress, and abnormal cytotrophoblastic invasion were higher compared to healthy pregnancies [19]. In particular, women with type 1 or type 2 DM were advised to use aspirin at a low dose of 60-150 mg/day (normal dose 81 mg/day) from the end of first trimester until delivery to reduce the risk of preeclampsia. The US Preventive Services Task Force recommended the use of low-dose aspirin (81 mg / day) as a prophylactic agent after 12 weeks of gestation in women at high risk of preeclampsia, based on the results of clinical trials [20]. Women with GDM have a increased risk of preterm labor, shoulder dystocia, polyhydramnios, urinary system and pelvic infection compared to the normal population [21]. It has been reported that if glycemic control is not achieved in GDM, the risk of stillbirth is increased 4-fold. In recent years, lower stillbirth rates have been observed with close follow-up of GDM and insulin treatment. In a study population consisting of women with GDM, the stillbirth rate was found to be about 1.4 per 1000 births [22, 23]. Although the mechanism of pregnancy induced retinopathy is not clearly demonstrated, it has a severe clinical course, so women who have previously type 1 or type 2 DM and planned to become pregnant or conceived should be informed about the risk of developing and/or progressing diabetic retinopathy. Comprehensive eye examinations should be performed before pregnancy or in the first trimester. Patients should also be followed-up in terms of grade of retinopathy in each trimester and within 1 year after birth [24].

Fetal Complications

Complications such as macrosomia, shoulder dystrophy, brachial plexus injury, spontaneous abortion, hyperbilirubinemia, neonatal hypoglycaemia, hypocalcemia, neonatal respiratory distress, hypertrophic cardiomyopathy and congenital malformations may be seen as a result of fetal hyperinsulinemia caused by maternal hyperglycemia in GDM [25]. According to the Pedersen hypothesis, the incidence of obesity and Type 2 DM in infants born from women with GDM was shown to be increased compared to those born from women without GDM due to effects of intrauterine hyperglycemia-related fetal β-cell hypertrophy on adipose tissue [26].

Screening and Diagnosis for GDM

Although there is no common consensus among GDM guidelines in the GDM screening, it is very important to determine the clinical risk in terms of GDM during the first visit of the patient during pregnancy, and to progress rapidly to screening if the patient has a high risk in order to prevent complications related to GDM [27].

Risk Factors for Gestatıonal Diabetes Mellitus [28]

•   The presence of GDM in prior pregnancy,
•   The diagnosis of glucose intolerance in the pre-pregnancy period,
•   A family history (especially in the first-degree relatives) of T2DM,
•   A history of macrosomia and polyhidramnios in the previous pregnancy,
•   Maternal wait gain (> 20 kg) in the previous pregnancy,
•   The presence of a fasting blood glucose level > 95 mg/dL and glucosuria,
•   Overweight (BMI > 25 kg /m2),
•   Advanced age (> 40 years),
•   Polycystic over syndrome

If the patient has one of the high risk factors in first prenatal visit, an oral glucose tolerance test (OGTT) should be performed based on the diagnostic criteria for diabetes mellitus in the non-pregnant population for unidentified diabetic patients [28].

Overt Diabetes Mellitus Diagnostic Criteria [28]

•   A fasting plasma glucose (≥ 8 hours fasting) level ≥ 126 mg/dL
•   OGTT second hour Plasma glucose PG ≥ 200 mg/dL (with 75 g glucose)
•   Random Plasma glucose PG ≥ 200 mg / dL + Symptoms of diabetes
•   HbA1c ≥ 6.5%

If high risk factors have not been identified, the recommendations of current guidelines are to make OGTT at 24-28 weeks in all pregnant women. The suggested approach for OGTT is pre-screening with a 50 g glucose test, switching to a 100 g glucose loading test if the 1- h glucose value is identified between 140-180 mg/dL. GDM is diagnosed if at least two values of the cut-off values of 95, 180, 155 and 140 of blood glucose levels at fasting, 1, 2 and 3-hours, respectively, in the 100-gr glucose loading test. If 50 g OGTT is higher than 180 mg/dL in the 1-hour blood glucose test, the patient is diagnosed directly with GDM without a 100 g blood glucose test [28]. Another approach recommended for diagnosis of GDM is one-step procedure using a 75 g OGTT. GDM can be diagnosed if at least one of the cut-off values of 92 mg/dL, 180 mg/dL and 153 mg/dL, respectively, of 0, 1 and 2 hours blood glucose levels are detected following a 75 g glucose loading glucose test. The one-step approach was proposed by the International Association of Diabetes and Pregnancy Study Groups (IADPSG) in 2010 and is still in use today. A 75 g OGTT is advantageous because the cut-off points are based on fetal complications of GDM [27]. In the American Diabetes Association (ADA) guidelines published in 2015, a one- or two-step approach is suggested based on selected community characteristics [30]. The approach adopted by the Society of Endocrinology and Metabolism of Turkey (SEMT) is the application of two-step diagnostic and screening criteria. SEMT recommends that at first two-step approach should be followed, as the 75-gram single-step OGTT may lead to pregnancies with a large number of GDM diagnoses and may cause financial problems [28].

Treatment

In order to control the maternal hyperglycemic state in GDM treatment, medical nutrition therapy (MNT), enhancement of physical activity and weight management programs are recommended. If blood

glucose level cannot be regulated with these lifestyle changes, additional medical treatment should be initiated [31].

Prevention of GDM

The prevalence of GDM is increasing and most of GDM patients have a history of type 1 and type 2 diabetes mellitus. There is an increase in GDM and type 2 diabetes in parallel with an increased risk of obesity worldwide. According to ADA 2018 guidelines, preconceptual counselling should be considered as an integral part of primary care for all diabetic patients in the age of fertility starting from the puberty period, family planning should be recommended and effective contraception should be provided for women with childbearing potential. Preconceptional counseling using appropriate training tools should prevent unplanned pregnancies and inform the patient about the complications that may occur in pregnancy due to poor glycemic control [24]. Preconceptional glycemic control as close to normal as possible [ideally HBA1C, below 6.5% (48 mmol/mol)] reduces the risk of congenital anomalies [24]. Pre-pregnancy obesity is a risk factor for GDM and it has been suggested that dietary counseling and lifestyle modification with physical activity in the pre-pregnancy period can cause a decrease in the incidence of GDM [32].

Medical Nutrition Therapy

In the ADA 2018 guidelines, it was suggested that an individualized nutrition plan should be developed by a dietitian who is a specialist in the management of GDM for medical nutrition therapy in GDM. Dietitian nutrition plans should focus on maintaining adequate maternal and fetal health, achieving glycemic goals, and ensuring adequate caloric intake to promote proper gestational weight gain. For all pregnant women, a daily meal plan including a minimum of 175 g carbohydrate, at least 71 g protein and 28 g fiber should be designed [24]. In women with GDM, the daily energy requirement is recommended as 24 kcal per day for ideal weight in obese pregnant women, 30 kcal at the first trimester and 35 kcal from the second trimester until delivery in non-obese pregnant women. The number of meals was recommended as 7 meals including main meals and collations [28].

Exercise

It has been reported that the regular exercise in GDM in conjunction with medical nutrition therapy would reduce the need for insulin, which increases insulin sensitivity [33]. In the American Congress of Obstetricians and Gynecologists (ACOG) 2018 guidelines, women with GDM were advised moderately aerobic exercise for at least 5 days for 30 minutes a week or for at least 150 minutes a week [34].

Medical Treatment

If hyperglycaemia cannot be controlled (a fasting plasma glucose level > 105 mg/dL or 1-hour postprandial >140 mg/dL) despite 2 weeks of medical nutrition therapy and exercise in GDM, medical treatment should be initiated [28]. It was stated that the most appropriate agent to choose in medical treatment is insulin and oral antidiabetics may be used in place of methformin and glyburidine [24]. Metformin has been shown to increase risk of prematurity, although the risk of newborn hypoglycemia is lower, and the risk of maternal weight gain is reported to be less than insulin [35-37]. The use of metformin, which is used for ovulation induction in women with policystic over syndrome, during pregnancy was also reported to have no benefit to prevent spontaneous abortion and GDM [38]. Gliburidine, another oral antidiabetic agent, has been shown to have a higher rate of neonatal hypoglycemia and macrosomia than insulin in the studies conducted [35]. Similarly, in a recent retrospective study of 110.879 women with GDM, neonatal comorbidities were more common in patients receiving glyburidine when compared to those treated with insulin [39]. NICE, ACOG and IDF guidelines have indicated that these two agents can be used safely and effectively during pregnancy [34, 40, 41] although the use of oral antidiabetic agents in the ADA guideline is limited due to limited safety in the long term [24]. Although there is no common consensus and there are different suggestions for the use of oral antidiabetic agents among guidelines, clinicians should determine the optimal treatment strategy by considering the risk-benefit profile of different treatments. The medicinally approved insulins in pregnancy include an intermediate acting human *NPH* and a long-acting insulin analogue *detemir*, a short-acting human regulatory insulin and rapid-acting analogues, insulin *aspart* and *lispro*.

A long-acting insulin analogue *glargine* and a rapid-acting insulin analogue *glulisine* have not yet been approved for use in pregnancy [42].

Individualized treatment should be planned when insulin therapy is to be started, because insulin dose may vary according to the patient's blood glucose level, weight, ethnicity and demographic characteristics. Insulin titration is often required to achieve targeted glucose levels due to physiological changes in pregnancy, and it is very important that the blood glucose is self-monitored on a daily basis [24]. There is usually a reduction in total daily insulin requirements during the first trimester and women, especially with type 1 diabetes, may experience increased hypoglycemia. In the second trimester, rapidly increasing insulin resistance requires an increase in insulin dose once or twice a week to achieve glycemic goals. Total insulin requirement can be planned as 0.7 U/kg/day in the first trimester, 0.8 U/kg/day in the second trimester, 0.9 U/kg/day in the third trimester, 1.0 U/kg in the term (36-40 weeks) and 1.5-2.0 U/kg in the severe obese women [43]. Generally, a daily total dose recommended includes less than 50% of the total dose should be given as basal insulin and more than 50% of the total dose as prandial insulin, and dose titration is necessary because there is usually a slight decrease in insulin requirements towards the end of the third trimester [24].

Treatment Targets and Postpartum Follow-Up

Suggested targets at GDM include a fasting blood sugar level of < 95 mg/dL, the 1- hour postprandial level of < 140 mg/dL, 2-hour postprandial level of < 120 mg/dL and HbA1c level of <6-6.5% [28]. If HbA1c can be achieved without risk of hypoglycaemia, <6% is the most appropriate targeted value, but if the risk o hypoglycemia is high, the targeted HbA1c can reach up to 7% [24]. National and international guidelines recommend long-term follow-up of women with GDM and all women with GDM history should receive 75 g glucose OGTT in terms of overt diabetes mellitus in postpartum 4-12 weeks. If plasma glucose (PG) concentrations in these assessments are normal, a new assessment should be made after 1-3 years, and patients should be trained in terms of symptoms of hyperglycemia and they should be advised to come to control if they experience such symptoms [24, 34].

CONCLUSION

As a result, GDM is a common complication that we frequently encounter in clinical practice of internal diseases and a disease that can cause severe problems in perinatal period and long term for both fetus and mother. Although there is no full consensus among international guidelines, the general approach is to screen pregnant women who have a high-risk on the first prenatal examination and all other pregnancies between 24-28 weeks for GDM. Early diagnosis and close follow-up should be aimed to reduce metabolic risks and prevent GDM-related complications.

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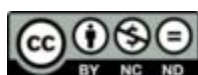gestational diabetes. JAMA Pediatr 2015;69:452-8.

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