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Diabates in pregnancy: diagnosis and treatment. Practice Guidelines of Turkish Perinatology Society

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Abstract

While the routine approach for the diagnosis of gestational diabetes is 50-g glucose tolerance test and 100-g OGTT in cases of a positive screen, a new approach was brought to agenda after it was found in the study of Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study that there is a linear relationship between blood glucose levels and gestational outcomes, and this was found to be closely associated with each value increase. It was shown that the approach of establishing diagnosis based on a single value at once with 75-g OGTT which is recently common in clinical practice helps 18% of pregnant population to get diagnosed, and the diet and exercise following the diagnosis improved gestational outcomes and affected gestational outcomes even in obese cases without gestational diabetes. Pregestational obesity having effect on gestational outcomes even though there is no diagnosis of gestational diabetes and finding that keeping weight gain during pregnancy under control is improving gestational outcomes reveal the importance of this matter. While 75-g OGTT procedure based on single value increases the number of cases who are established the diagnosis of gestational diabetes compared to the two-step screening and diagnosis test, diet-exercise practice in cases with such diagnosis is a condition which keeps weight gain during pregnancy under control and also has a positive impact on gestational outcomes. Glycemia being above the desired range with 1–2 weeks of follow-up of the blood glucose will require medical treatment. This is an expected and desired target. Therefore, applying 75-g OGTT based on single value has become the new clinical practice and it is recommended. This clinical practice guideline was prepared by the Diabetes and Pregnancy Study Group of Turkish Perinatology Society.

Keywords: Diabetes, OGTT, pregnancy.

Özet: Gebelikte diyabet: Tanı ve tedavi. Türk Perinatoloji Derneği Uygulama Rehberi

Gebelik diyabetinin tanınmasında 50 g glukoz tarama testi ve pozitif tarama olgularında 100 g OGTT ile tanının sağlanması uygulanmakta olan bir yaklaşım iken, *Hyperglycemia and Adverse Pregnancy Outcome* (HAPO) çalışması sonucu kan şekeri düzeyleri ile gebelik sonuçları arasında doğrusal ilişki olduğu, bunun da her değer artışı ile yakın ilişkili bulunduğunun saptanmasından sonra, yeni bir yaklaşım gündeme gelmiştir. Giderek klinik uygulamada yer bulan 75 g OGTT ile tek seferde ve tek değere dayalı tanı konulması yaklaşımı, gebe popülasyonunun %18'ine tanı koydurmakla beraber, sonrasında yapılan diyet ve egzersiz uygulamasının, gebelik sonuçlarını iyileştirdiği ve hatta gebelik diyabeti tanısı almayan obez olgularda bile gebelik sonuçlarını olumlu etkilediği ortaya konulmuştur. Gebelik öncesi obezitenin gebelik sonuçları üzerine, gebelik diyabeti tanısı olmadığı halde, etkili olması ve gebelikte kilo artışının kontrol altına alınmasının gebelik sonuçlarını iyileştirmesinin saptanması, konunun önemini daha da gözler önüne sermektedir. Tek değere dayalı 75 g OGTT uygulaması, iki aşamalı önce tarama ve akabinde tanı testi uygulamasına oranla gebelik diyabeti tanısı alan olgu sayısını artırmakla beraber; bu tanıyı alan olgularda diyet-egzersiz uygulamasının, gebede kilo artışını kontrol altına alan ve ayrıca gebelik sonuçları üzerine olumlu etki sağlayan bir durumdur. Kan şekerinin 1–2 haftalık izlemleri ile gliseminin istenen sınırların üzerinde olması, medikal tedaviyi gerektirecektir. Bu ise beklenen ve istenen bir hedef olmaktadır. Bu nedenlerle, her gebeye tek değere dayalı 75 g OGTT uygulanması yeni klinik uygulama olarak yerini almıştır ve tavsiye edilmektedir. Bu klinik uygulama rehberi, Türk Perinatoloji Derneği Diyabet ve Gebelik Çalışma Grubu tarafından hazırlanmıştır.

Anahtar sözcükler: Diyabet, gebelik, OGTT.

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This clinical practice guideline was prepared by the Diabetes and Pregnancy Study Group of Turkish Perinatology Society to clarify controversial issues in Turkey and facilitate clinical practice in the light of new scientific data obtained on pregnancy and diabetes recently.

Gestational diabetes (GD) which is one of the most common medical complications of pregnancy is "the dysfunction of glucose metabolism which develops in the second half of pregnancy and disappears when pregnancy ends".[1] Dysfunction of glucose metabolism may have various levels. While diet is sufficient generally, some may need insulin.

In the common definition made by IADSPG (The International Association of Diabetes and Pregnancy Study Group), WHO (The World Health Organization) and ADA (The American Diabetes Association), those who are pregestational diabetic and noticed during the pregnancy for the first time were distinguished from the diabetes cases developing during pregnancy, and two different definitions were set as "gestational diabetes" and "overt diabetes".[2–4] In this case, "gestational diabetes" defines the change which really appears during pregnancy and is diagnosed at the second half of pregnancy by tests and developing in the presence of "pancreas which cannot deal with the diabetogenic changes" of pregnancy.[5] The pregnancy itself is the condition of "physiological insulin resistance". "Overt diabetes" defines the diabetes cases which have the metabolic processes at the early periods of pregnancy almost same with non-gestational condition, and identified even in the first trimester where insulin resistance is not clear yet. The cases which do not meet "overt diabetes" criteria in the tests performed during gestational period but not found to have a normal carbohydrate metabolism, either, are diagnosed as "gestational diabetes" and their follow-up and treatment are carried out accordingly.

Prevalence

About 3–25% of pregnant women are established with GD diagnosis.[6] The main reason for different GD incidence rates among the population investigated is the difference in the incidence rate of Type 2 diabetes mellitus (DM) in the society.[7] Also, maternal obesity increasing at young ages, decreased physical activity, increased consumption of convenience food, and advanced maternal age and race are other factors which have impact on prevalence.[7] At the same time, the differences in GD screening models, the threshold values used, and diagnostic criteria create differences in GD prevalence. However, even though different methods and diagnostic criteria are used, it is definite that the prevalence of Type 2 DM and also GD has increased in time highly, especially within last 20 years.[5,8]

Pathophysiology and Risk Factors

Together with pregnancy, endocrine and metabolic changes occur right after conception. The main purpose of these changes occurring in maternal metabolism is to provide sufficient nutrient to fetus.[9] Particularly in the last trimester where fetal growth is the fastest and therefore fetal nutrition need is the highest, the changes in maternal carbonhydrate and lipid metabolism become more distinct. During pregnancy, plasma levels of lipolytic hormones increase and generally maternal fat use elevates, "glucose" is for the use of fetus basically.[9] Maternal insulin resistance begins at second trimester with the effect of metabolic and hormonal changes and becomes distinctive at third trimester. In this way, insulin resistance increases much more with the increase of the levels of hPL (human placental lactogen), hPGH (human placental growth hormone), estrogen, progesterone, CRH, cortisol, prolactin, somatostatin and probably tumor necrosis factor (TNF-α) that have diabetogenic effects. All these changes reach their peak level approximately at the 30 weeks of gestation. Insulin resistance which develops as a result of normal physiological changes during pregnancy is required for sufficient nutrition and growth of fetus.[9] Since maternal pancreas cannot deal with this situation when increased insulin resistance is encountered, these physiological changes result in GD which is a pathological condition.[5] In fact, pathophysiological mechanisms developing in the formation of GD show similarities substantially with Type 2 DM. In both cases, a substantial increase occurs in the insulin resistance as the week of gestation advances and insulin response is not sufficient.

Risk factors for gestational diabetes are defined and it was asserted to perform glucose screening/diagnostic tests in pregnant women having these risk factors. These risk factors are listed in **Table 1**.

Table 1. Risk factors for gestational diabetes.

- Type 2 DM history in the family (especially in first degree relatives) [10,11]
- GD history in previous pregnancy[11]
- Obesity (body mass index, BMI ≥30/m^2)[10–12]
  - It is remarkable that 60–80% of GD cases are obese. Also, GD risk increases as BMI increases.[11] Cardiometabolic risk factors such as pregestational hypertension and borderline high blood pressure values were also associated with increased GD risk.[12]
  - Obesity is associated with inflammatory changes. There is an increase in inflammatory cytokines, especially in the levels of TNF-α, IL-6, NFκB, PAI-1 and CRP.[13] Glucose levels chronically increased with obesity cause the modification of building blocks such as nucleic acids and proteins into advanced glycation end products (AGE). The accumulation of AGE which is fast and higher than physiological levels causes permanent damages in the tissues. Today, AGE formation is held responsible in the physiopathology of many diseases in diabetes cases including neurodegenerative diseases, metabolic syndrome and vasculopathies.[14] As a respond to AGE formation, a series of inflammatory response is initiated with NFκB pathway, and the tissue damage created with the activation of T-cells and the release of inflammatory cytokines in particular results with vasculopathy and fibrosis.[15,16] Therefore, the development of complications such as myocardial infarction (MI), atherosclerosis, stroke etc. is not a surprise in obesity and DM patients.[16] The same mechanism may explain the appearance of vascular complications basically such as insufficient placentation, preeclampsia, IUGR, sudden infant death under poor conditions caused by chronic hyperglycemia as well as obesity during pregnancy.
- Obesity is a preventable risk factor. Therefore, it should be taken seriously and patient should be informed during preconceptional period and ensured to lose weight.
- Ethnical group[10,11]
  - In the diabetes prevalence studies performed in Turkey, DM prevalence was found as 13.7% according to the results of TURDEP-II performed with the participation of 26,000 individuals who were 20-year-old and above in 2010.[17] Almost half of the cases in Diabetes Mellitus group consist of newly-diagnosed cases. Diabetes prevalence varies according to the regions in Turkey. While Northern Anatolia Region has the lowest prevalence rate (14.5%), Eastern Anatolia Region has the highest prevalence rate (18.2%). Eastern Anatolia Region was found to be the region with the lowest awareness for diabetes as well as the region having the highest prevalence rate.[17]
  - Compared to TURDEP-I[18] study performed in 1998, the results found by TURDEP-II prevalence study showed that the diabetes prevalence rate increased for 90% and obesity for 44% in Turkey.[17]
  - Another issue revealed by TURDEP-II study is that diabetes prevalence rate increased significantly in those who are in reproductive period.[17]
  - Considering the world population, diabetes prevalence is about 8.4%.[19] In the light of these data, our country is among the regions with the highest prevalence according to comparative worldwide diabetes prevalence studies.
  - It is known that GD prevalence is high among those originated from South Asia, black Caribbean and Middle East.
- Being older than 25.[10]
- Smoking[10]
- Macrosomic infant history[5,11]
- History of unexplained perinatal loss and baby with malformation[5]
- Maternal birth weight being >4.1 kg or <2.7 kg[5]
- A medical condition that will cause susceptibility to diabetes development (such as Cushing's syndrome, polycystic ovary syndrome, glucocorticoid use, presence of hypertension etc.)[5]
- Gaining too much weight between pregnancies or during pregnancy.[5,11]
- Multiple pregnancy[11]
- Short height[11]
- Sedentary life-style[11]

When planning gestational diabetes screening program, the characteristics of the population under investigation are also important. For instance, only 10% of the population in the USA is evaluated within low risk group. Therefore, it is wise to perform tests on every pregnant woman instead of carrying out a risk-oriented screening in the USA.[20] Besides, considering the risk factors mentioned above, there are few pregnant women left. Hence, it does not seem logical to perform screening based on risk factors.

Screening and Diagnosis: Why Important?

Clinically identifying gestational diabetes is significant basically for preventing gestational complications, improving fetal and neonatal outcomes and to prevent its long-term effects on next generations. While some of the complications developing associated with GD appear in the early period, some of them are seen in the long-term. Preterm labor, macrosomia, birth trauma and sudden infant death can be listed among the fetal complications associated with GD.[21–23] Among the early complications in the newborns of GD mothers, there are polycythemia, hyperviscosity, hypoglycemia, hypocalcemia, hyperbilirubinemi, respiratory distress syndrome (RDS).[24,25] Among the long-term complications, obesity, metabolic syndrome, Type 2 DM and increase in hyperactivity prevalence were found in the infants of GD mothers.[26,27] Preeclampsia risk, increased operative labor risk and polyhydramnios can be listed among the maternal risks.[28,29] Also, the risk for Type 2 DM, metabolic syndrome and coronary artery disease increased in the long-term in GD mothers.[30,31]

Identifying GD in the early period decreases preeclampsia risk for 40% and macrosomic infant risk for 50%. Additionally, shoulder dystocia and brachial plexus palsy risks decrease for 60%. Early detection of GD also decreases stillbirth risk.[32]

Frequent Obstetric and Perinatal Problems in Gestational Diabetes

It is known that the presence of chronic hyperglycemia ongoing especially in the last 4–6 weeks of gestation is associated with sudden fetal death associated with possible acidosis even in normal fetuses anatomically.[33,34] Even in GD cases with well-controlled metabolism, fetal macromosia, neonatal hypoglycemia, polycytemia and

jaundice risks increased although there is no increase in perinatal mortality.[21] Also, cesarean section is recommended when estimated fetal weight is ≥4500 g.[1]

Macrosomia

It is the most common complication seen in gestational diabetes. Maternal factors associated with macrosomia are hyperglycemia, mother being overweight, being obese during pregnancy (>18 kg), advanced maternal age and multiparity.[35,36] While the rate of women delivering baby over 4500 g is 2% in the general obstetric population, it is 4% among women with GD diagnosis.[37] It is reported that 20–30% of the infants of women with GD diagnosis but not undergoing treatment born above 4000 g.[38]

Fetal growth rate increases particularly in the second half of pregnancy. Maternal hyperglycemia (postprandial hyperglycemia in particular) in this period causes fetal hyperinsulinemia and fetal growth is triggered. Macrosomic fetuses of diabetic pregnant women are different anthropometrically from the macrosomic fetuses of normal pregnant women. There is excessive fat accumulation in the shoulders and bodies of these fetuses. This increases the prevalence of shoulder dystocia, brachial plexus injuries and clavicle fracture.[39] Similarly, cephalopelvic disproportion resulted in cesarean section is more frequent. Macrosomia is closely associated with neonatal hypoglycemia in particular. Unexplained sudden intrauterine death near term and asymmetric septal hypertrophy causing cardiac ventricle dysfunction are more frequent in these infants.[40]

Shoulder Dystocia and Birth Trauma

Macrosomia causes increase in the prevalence of shoulder dystocia which may result in brachial plexus injury and clavicular fractures in newborns of patients with GD. The prevalence of shoulder dystocia is 6–10 times higher in the infants of diabetic mothers.[1] Brachial plexus injuries may cause a permanent damage in 5–22% of the babies.[41]

Interventional and Cesarean Deliveries

The rates of interventional and cesarean deliveries have increased depending on macrosomia, intrauterine growth restriction (IUGR) and presentation anomalies. The rate of cesarean is even higher in macrosomic fetuses in cases where glucose control cannot be established adequately. As the diabetes control gets worse, the cesarean rate increases accordingly. The most significant factors here except fetal weight are the failure of labor induction and fetal asphyxia. Cesarean section is recommended in diabetic pregnancies with fetal weights estimated 4000 g and above.[1] Normal vaginal delivery is recommended in other cases, and applying cervical prostaglandin in cases where labor induction is required is the only logical method to choose.

Timing of delivery is also a problematic issue for diabetic pregnancies. In cases with pregestational diabetes where glucose is well controlled, planning delivery after 39 weeks is suitable.[42] However, either with or without insulin, no safe delivery week has been determined to recommend in the perspective of evidence-based medicine for GD cases.[1] Therefore, 39 weeks of gestation should be aimed as in cases with overt diabetes.

The frequency of fetal well-being tests is quite controversial. In GD cases with well-controlled metabolism, each physician and clinic may decide according to their own practices. However, GD and pregestational diabetes cases with poor glycemic control are under risk in terms of fetal asphyxia and the tests showing fetal well-being should certainly be performed in this group.[1] Tests showing fetal well-being can be begun between 28 and 32 weeks according to the glycemic control medical complications (nephropathy, vasculopathy etc.) of patients.

Hypertension - Preeclampsia

They develop particularly during the late periods of pregnancy. While the association between gestational diabetes and preeclampsia is revealed, the responsible mechanisms are still unclear. It is considered that the endothelial dysfunction in such cases cannot produce prostacycline (PGI2) sufficient enough to meet elevated angiotensin-2 and vasopressine. It is seen in 5–10% in all pregnancies. Preeclampsia is seen more frequently in diabetic pregnant women with vascular problems such as proteinuria in particular. The increase of perinatal mortality is 20 times higher than those with nor-

mal blood pressure and it is considered as the main reason for maternal and fetal loss. While the relationship of insulin resistance with high blood pressure and obesity was shown and this relationship was clearly defined in men and non-pregnant women, the relationship of glucose intolerance with the problems concurrent with hypertension in pregnant women could not be determined with so accurate borders.[43] In the studies performed, mean artery blood pressures of patients whose gestational diabetes is found in the early periods of pregnancy and requiring insulin treatment were higher than the patients with normal glucose tolerance and are regulated with diet. Also, there are authors claiming that pregnancy-induced hypertension is the clinical reflection of insulin resistance. The relationship between increasing glucose level and the severity of preeclampsia has been shown in the studies.[44] This problem is also the main reason of the premature labor in diabetic pregnant women. Today, findings have been accumulating and it is considered that the insulin resistance has a role in the development of preeclampsia, at least partially. It can be also thought that treating insulin resistance with this mechanism will decrease preeclampsia risk and even other anti-inflammatory effects of balancing carbohydrate metabolism of insulin may be protective against the development of preeclampsia. In a meta-analysis including 11 randomized controlled studies, the effects of insulin and metformin treatment were compared and a significant decrease was found in the pregnancy-induced hypertension with metformin treatment. Also, no difference was found in terms of preeclampsia between the groups undergoing insulin or metformin treatment. Therefore, the activities of insulin and metformin were found similar on the prevalence of preeclampsia in terms of treatment activity.[45]

Polyhydramnios

Polyhydramnios is seen in about 1/3 of the diabetic pregnancies. In such case, pregnant women should definitely be evaluated in terms of fetal malformations (particularly for the malformations of central nervous system and gastrointestinal system). However, it is considered that the presence of polyhydramnios in diabetic cases does not cause an additional increase in perinatal morbidity or mortality.[46]

Neonatal Metabolic Disorders

The prevalence of hypoglycemia, hypocalcemia, hypomagnesemia, polycythemia and hyperbilirubinemia of babies born from women with gestational diabates is increased.

Hypoglycemia

The incidence rate of hypoglycemia was found as 25–40%.[47] The incidence rate of hypoglycemia was reported high also in mothers with well-controlled plasma glucose concentration.[48] It is considered that intrapartum glycemic control in particular determines the hypoglycemia risk of newborn. If hypoglycemia is not detected and intervened on time, it may lead to seizure, coma and brain damage. Therefore, glucose follow-up should be monitored carefully following the delivery until it is ensured that the metabolic control of the infant of diabetic mother.

Polycythemia and hyperviscosity

It is seen in 5–10% of diabetic pregnant women and closely related with glycemic control. Due to the decrease in oxygenation, erythropoietin levels of the umbilical cords of infants of diabetic mothers are typically high and therefore the rate of polycythemia is increased in such infants.[24] Polycythemia leads to increase in the prevalence of postnatal hyperbilirubinemia and this also causes the increase in phototherapy need.[41] Another potential problem is the tissue damage and ischemia associated with hyperviscosity.[6]

Neonatal hypocalcemia and hyperbilirubinemia

Neonatal hypocalcemia is a problem seen almost in 50% of the infants of diabetic mothers. It usually appears in the first 3 days of life. The incidence of hyperbilirubinemia is two times higher than health pregnancies and found 25% of the infants of diabetic mothers.[6] Another reason is the preterm labor associated with diabetes.

Postnatal Long-term Risks

Long-term risks for mother

Diabetes develops in about half of the women with gestational diabetes within 22–28 years in the future.[1] How short will the diabetes develop depends on the personal risk factors. Risks such as ethnic group, obesity, age and polycystic ovarian syndrome cause diabetes to develop

faster. The possibility of developing Type 2 DM in patients requiring insulin during pregnancy is higher.[49] For example, diabetes develops within 5 years following the pregnancy in 60% of Latin American women.[1]

It was found in the studies performed that those with gestational diabetes were under risk also in terms of metabolic syndrome, atherosclerosis and cardiovascular dysfunction after postpartum third month.[50]

Hyperinsulinemia during pregnancy displays 30–50% decrease just after delivery. The decrease slowly continues within following 6–12 weeks. Blood glucose levels return to normal levels in the early postnatal period in most of the patients with GD. Therefore, evaluating patients between postpartum 6 and 12 weeks in terms of glucose metabolism is very important for determining the risk for the development of Type 2 DM within following 5–10 years and establishing patient follow-up strategy.[51,52]

Long-term risks for fetus

The investigators monitoring the infants of diabetic mothers for future diabetes development reported that diabetes develop in such infants 20 times more than the infants of non-diabetic mothers.[42] Obesity prevalence is also increased in these infants. The mechanisms of maternal diabetes leading to future obesity in fetus are not known clearly. In a prospective study comparing the infants of GD, Type 1 DM and non-diabetic pregnant women, it was found that more than 1/3 of the babies born from women with GD were overweight or obese when they reach 11-year-old. This rate was found to be two times higher than those delivered by Type 1 DM or non-diabetic women.[53,54] Also, as another important point of this study, it was found that the maternal obesity during early pregnancy period is the most significant factor determining the risk for infants of women with GD being overweight at 2-, 8- and 11-year-old (and therefore the insulin resistance at early period). It was reported that smoking during pregnancy is also associated with the risk for childhood obesity. This result was found independent from GD treatment and macrosomic birth.[54] The results of this study are remarkable for revealing how the preventable reasons of obesity becoming a serious public health issue is important.

In the HAPO (Hyperglycemia and Adverse Pregnancy Outcome) study, which is one of the most significant studies on gestational diabetes performed, the effect of being obese on fetal birth weight was found to be an additional 174 g, it was 339 g in pregnant women who were GD.[55]

Four groups were created in a cohort study investigating the risk factors for metabolic syndrome (obesity, hypertension, dyslipidemia, glucose intolerance) during childhood.[27] The groups were macrosomic baby and normal glucose tolerance (LGA+control), macrosomic baby and GD (LGA+GD), normal birth weight and normal glucose tolerance (AGA+control), and normal birth weight and GD (AGA+GD). The development of insulin resistance during childhood was found 10 times higher in LGA+GD group. The risk of developing metabolic syndrome at any period was not found to be different in LGA and AGA control group, but it was found 3.6 times higher in LGA+GD group than AGA+GD group.[27]

It was found in the studies performed that the children of women with pregestational and gestational diabetes had higher rates of attention-deficit hyperactivity disorder and weaker motor functions during school ages. No change was observed in cognitive functions.[6]

Benefits of Glucose Tests

The purpose of screening tests during pregnancy is not to diagnose but to determine the group under risk. It is still controversial if it is necessary to carry out diabetes screening during pregnancy or not, if it should be done to all pregnant women or only those under risk, and which method will be used for these tests. However, current data with the evidence-based medicine perspective show us that performing screening and diagnostic tests for GD is very significant in order to identify GD and do appropriate management plans, to decrease early period neonatal and maternal morbidities such as macrosomia, shoulder dystocia and preeclampsia and to determine metabolic syndrome and related risks on time which are expected for mother and infant in the long-term.

Screening and diagnostic tests performed in the second trimester are done according to preferred test or by drinking 75-g liquid containing glucose as a single step test or 50-g and then 100-g if necessary as a two-step test and then evaluating venous plasma blood sample. These tests have no serious maternal or fetal effects. Only certain patients may have problem for consuming hyperosmolar liquid (more distinct in 100-

g glucose).[5] Therefore, 75-g glucose tolerance test is considered as diagnostic test at a single step.

When test results indicate GD, first the diet-exercise is planned according to the week of gestation and then medical treatment later if necessary. Also, the family should be informed about perinatal risks that are associated with GD and fetal monitorization is required in case of necessity and the increase of prenatal examination frequency.[5] In a study in which the cases with and without screening were modeled, it was shown that performing the test in populations with high GD and Type 2 DM prevalence was beneficial both for preventing Type 2 DM and costs.[44] Without any significant decrease in the number of patients which are required to be evaluated with laboratory screening method, not screening patients with low risk may lead to overlook some patients with GD.

Glucose Tests

Maternal venous plasma changes under normal conditions are as follows when performing glucose tolerance test: preprandial blood glucose (PBG) is between 80 and 90 mg/dl. Within approximately 4–5 minutes, the solution containing 75-g glucose is drunk and BG level increases up to 130–140 mg/dl within 30–40 minutes, it decreases slightly below PBG level within 120–150 minutes; at the end of 180 minutes, PBG level is reached.[56,57] In the individuals with normal carbohydrate metabolism, normal glucose levels are reached within about 2 hours. These tests have no risk for fetuses.[5]

It is still debated which screening should be done for GD (screening everyone or risk-based approach) and which test should be used.[58] The reason for this dispute is that there is no distinct definition in the world in terms of the criteria for screening everyone and it is not clear which glucose intolerance case will provide treatment benefit. At this point, screening test should be selected by considering the purposes of screening and cost-benefit balance.

There are publications stating that GD diagnosis is delayed and there are high false results which are about 10–20% by applying 100-g OGGT to those who had abnormal results from 50-g glucose test.[59]

There is difference of opinion on the threshold value of 50-g glucose tolerance test. When threshold value is considered as 140 mg/dl, 3-hour OGTT is performed in 10–15% of cases and GD is detected in 20–40% of the cases who undergo diagnostic test. With 140 mg/dl threshold value, the sensitivity was calculated as 80% and specificity as 90%, and the diagnosis of approximately 20% of the cases are overlooked.[59]

In 10% of the cases, serum glucose level in glucose tolerance test is between 130 and 140 mg/dl. Therefore, when the threshold value is decreased to 130 mg/dl in glucose tolerance test, the sensitivity of the test increases to 90; however, the number of patients referred to diagnostic tests increases for 60%. In a study conducted in 2002, the sensitivity and specificity values were identified for GD screening methods and these values were given in **Table 2**.[60] Finally, ADA and ACOG recommend glucose threshold value in serum as 140 mg/dl.[1,2]

Two-Step Glucose Test

Threshold values checked in venous serum and evaluation of 50-g GTT are as below:[1] No diagnostic test is required for 50-g GTT <140 mg/dl. In this case, negative predictive value is about 85–90%. So, the risk for overlooking GD in glucose values below 140 mg/dl is 10–15%.[1]

If 50-g GTT is between 140–180 mg/dl, diagnostic 3-hour 100-g OGTT is applied. GD diagnosis is established in case that two of the values are positive in 100-g OGTT: If PBG is >95 mg/dl, 1-hour BG is >180 mg/dl, 2-hour BG is >155 mg/dl, 3-hour BG is >140 mg/dl and 50-g GTT is ≥180 mg/dl, the patient is directly established GD diagnosis and the treatment is initiated.

Single-Step Glucose Test

In 2010, IADPSG (International Association of Diabetes and Pregnancy Study Group) recommended new criteria for GD diagnosis. These diagnosis criteria

Table 2. Sensitivity and specificity of the methods used in GD diagnosis.[60]

Screening method	Sensitivity (%)	Selectivity (%)
Risk factors	50	66
Random glucose measurement	40	90
HbA1c	40	90
50-g GTT (1-hour 140 mg/dl)	59	91
75-g OGTT	79	83

was determined with HAPO study where the results of multinational 25,000 pregnant women were investigated.[61] New IADPSG criteria were mainly prepared by focusing on the perinatal risk of parameters which are >90 percentile. Accordingly, it is recommended to check PBG and HbA1c or spot blood glucose (sBG). If PBG is >126 mg/dl and HbA1c is >6.5% or sBG is >200 mg/dl, it is recommended to consider it as overt diabetes and treat accordingly. If the results are not consistent with overt diabetes, but PBG is ≥92 mg/dl yet below 126 mg/dl, it is recommended to treat by considering it as GD. If PBG is below 92 mg/dl, it is recommended to test with 75-g OGTT between 24 and 28 weeks of gestation. The diagnosis criteria of 75-g OGTT can be listed as follows: If PBG is below 126 mg/dl, it is consistent with overt diabetes. If at least one of the values below is positive, it is consistent with GD diagnosis: PBG ≥92 mg/dl, 1-hour BG ≥180 mg/dl and 2-hour BG ≥153 mg/dl.

Which Glucose Test Should We Do?

IADPSG criteria differ with the recommendation that performing screening in the first trimester according to the algorithms used previously and testing with 75-g OGTT again in the second trimester if the result is negative in the first one.[2] ACOG recommends carrying out screening in the risk group during the first trimester. When IADPSG criteria were applied, the rate of diagnosed GD cases increased to 18% but they were not adopted by ACOG.[1]

Since there was no optimal approach for the diagnosis of gestational diabetes, NIH (National Institutes of Health) held a consensus meeting with the aim of determining the most appropriate diagnostic approach.[32] The results of related 97 studies (6 randomized controlled studies, 63 prospective cohort studies and 28 retrospective cohort studies) were investigated and continuous and positive relationship was found between increasing glucose values and macrosomia, and between primary cesarean rates and increasing glucose values at 75-g OGTT. 50-g OGTT has higher negative predictive value as well as suboptimal positive predictive values.

It was reported in a prospective randomized controlled study doing cost analysis by comparing single-step and two-step screening that two-step screening is more convenient for costs.[62] The cost difference being not so much, and applying diet-exercise program to a wider pregnancy group providing positive effects not only on glucose levels but also gestational outcomes should not be overlooked.

Since Type 2 diabetes is frequently seen in Turkey, it can be tolerated easily and done at a single step and it is also a diagnostic test, applying 75-g OGTT based on single value positivity to all pregnant women should be addressed as the most appropriate approach.

To Whom and When to Apply Glucose Test?

In the United States of America, it is logical to screen each pregnant woman since they have at least one of the risk factors that may have an affect on balancing carbohydrate metabolism during pregnancy in 90% of pregnant women.[1] Also, there is no risk factor in about 20% of pregnant women found to have GD.[5] As a result of the systematic review done by USPSTF (States Preventive Services Task Force), it was stated that it is required to screen everyone after 24 weeks of gestation, but it does not help to screen everyone during early gestation period and that it is more significant to perform risk-based screening during the first prenatal visit.[61]

If the patient has a risk factor for Type 2 DM (obesity, BMI ≥30 kg/m^2, history of GD or impaired glucose metabolism, polycystic ovarian syndrome etc.), screening during the first prenatal visit would be a logical approach.[5] Performing PBG evaluation in the risk group during first antenatal visit and 75-g OGTT during 24–26 weeks of gestation if PBG is <92 mg/dl would be more appropriate. If the first screening is

Table 3. Points to consider in OGTT.

- The test should be carried out in the morning.
- Fasting is required for at least 8 hours and max. 14 hours.
- Patient should be on diet for at least 3 days uninterruptedly (min. 150 mg carbohydrate daily). If pregnant woman is on a diet poor for carbohydrate before the test, the insulin response to the test is less than the expected and false positivity rate increases.
- During the test, pregnant woman should be in sitting position and should not make any effort.
- Pregnant woman should not smoke for 12 hours before the test.
- Patient should rest for 30 minutes before preprandial glucose measurement.
- After preprandial glucose measurement, patient should drink 75-g glucose solution within 5 minutes.

negative or no screening is performed in the early period, the screening should be carried out at 24–28 weeks of gestation.[5]

There are some matters to consider when conducting glucose tolerance tests (**Table 3**). It is significant to provide an environment close to basic physiological conditions in order to standardize tests and measurements and to rule out other factors.

What to Do in Pregnant Women Who Cannot Tolerate Oral Glucose Test?

Performing serial glucose measurement would be logical approach in order to rule out hyperglycemic conditions in pregnant women who cannot tolerate standard oral glucose tolerance test.[5] In pregnant women who have risk factors for GD in particular and cannot tolerate screening tests, it is necessary to perform random PBG and postprandial BG measurements. This approach is also convenient for patients who underwent gastric bypass operation.[5] According to the review of Coustan et al., GD risk is very low in pregnant women whose PBG is lower than 85 mg/dl at 24 weeks of gestation.[61] However, additional tests and measurements are required in values above this value.[5]

Also, the methods such as glucose screening in urine and random blood glucose measurement were evaluated in terms of screening activity but no significant result was found. HbA1c is significant for evaluating treatment activity rather than screening and it gives information about metabolic process for at least 60 days.

HbA1c

In the studies performed, a proper threshold value with good sensitivity and specificity during GD screening could not be found for HbA1c. In four different studies conducted on this matter, HbA1c threshold values were found 5.0, 5.3, 5.5 and 7.5, but no clear result was obtained for detecting GD according to these values.[63–66] In the study of Agarwal et al. performed on 442 patients, it was concluded that HbA1c is a weak test for GD screening.[63] The population size in the study of Uncu et al. was 42 pregnant women and it was stated that HbA1c did not provide any additional contribution.[64] For the reasons such as inconsistencies in the standardization of HbA1c, failure to measure at all clinics, technical problems and high costs, it does not seem convenient to use it in Turkey for screening purposes. However, it is accepted as the "golden standard" for the follow-up of glycemic control.

In regions where healthcare service cannot be provided sufficiently, checking PBG between 24 and 28 weeks of gestation can be a practical approach. In a study conducted in China by compiling the data of 15 hospitals where 24,584 pregnant women were screened, it was reported that performing diagnostic 75g OGTT on pregnant women whose PBG is between 4.4 and 5.0 mmol/L (79–90 mg/dL) will reduce the requirement of 2-hour diagnostic test by half.[65] However, when applying screening tests, a specific approach should be determined by considering the characteristics of population. It cannot be generalized in this study since ethnical characteristics affect Type 2 DM prevalence and also different threshold values were used in the study conducted in China.[67]

May Glucose Tests be Harmful for Mother and Fetus?

It was shown that consuming concentrated hyperosmolar glucose solutions for GD screening and diagnostic tests may cause gastrointestinal osmotic imbalance which results with gastric irritation, delay in gastric discharge, nausea, and vomiting in less number of patients.[5] In a study performed by Agarwal et al., it was reported that 9.8% of 5142 pregnant women could not complete 100-g OGTT. The major reason for being unable to complete the test was the vomiting of pregnant women. In 2% of the cases, various reasons were found such as children of pregnant women drinking the solution, eating food during test, not giving blood at required times and being unable to complete test in term of time.[68] It was reported that OGTT has no side effects other than those stated above.[5,69]

2014 Cochrane Review: Different Results?

In the Cochrane[70] review performed in 2014 and investigated the impact of GD screening on improving the health of mother and neonate, few high quality evidences on the improvement of maternal and neonatal health by GD screening were found based on the data of 3972 women and 4 studies (Bergus and Murphy, 1992; Murphy et al., 1994; Griffin et al., 2000; Martinez Collado et al., 2003) which were consistent with the criteria among 31 studies.[71–74] These studies were carried

out in limited regions. When thinking on GD risk and screening approach, the characteristics of the population investigated (such as ethnic group, nourishment habits etc.) should be considered and interpreted accordingly. It would be useful to assess carefully these studies included in 2014 Cochrane review by considering their weak aspects and to remain distant towards the results and interpretations of this review in the current situation.

Consequently, it seen that further studies are required to determine which screening would be more appropriate. Since only a particular part of the pregnant population screened is established GD diagnosis, it is required to do sub-group analyses which are statistically powerful to do comparison and have sufficient population. Also, other studies are required for determining the activity of other methods (such as capillary blood sugar test, glucosuria etc.) which can be used instead of glucose tolerance tests that are applied simpler yet cannot be tolerated by some patients.[70]

HAPO Study: Why Important?

HAPO study is an epidemiological research designed to seek an answer about how various levels of glucose intolerance affects fetal and perinatal outcomes during pregnancies. It is a study planned internationally and including 25,505 pregnant women from various ethnical groups. Its primary results were determined as macrosomia, primary cesarean rate, neonatal hypoglycemia and hyperinsulinemia. Preterm labor, preeclampsia, newborn intensive care unit, shoulder dystocia, birth trauma and neonatal adiposity were considered as secondary results.[75] A continuous relationship was found between glucose levels (even below maternal diabetes limits) and perinatal outcomes such as birth weight and umbilical cord C-peptide levels. While there is no particular threshold glucose level in predicting gestational outcomes, it was found that there is a direct association with gestational outcomes and complications as preprandial or 1-hour and 2-hour glucose levels increase (even within normal limits). Even though the outcomes of this study are below overt diabetes levels, the more blood glucose levels are kept under control, the more it reflects positively to the gestational outcomes.

However, observing poor gestational outcomes also in pre- and postprandial blood glucose levels that is identified within "normal" levels make us consider that new threshold values should be used in screening models. In the light of the results of HAPO study, new IADPSG criteria were defined.[76] While single positive value being sufficient for the diagnosis and also the threshold values being slightly lower increase the sensitivity in the new IADPSG criteria, the prevalence of diagnosed GD cases increase to 18%.[1] These threshold values correspond to mean glucose levels where birth weight, umbilical cord C-peptide levels and macrosomia risk increase for 1.75 times. In cases established with GD diagnosis according to these threshold values, macrosomia, preeclampsia and preterm labor risks increase 2 times. However, further studies are needed to get more information how gestational outcomes will improve or if they will improve or not depending on the treatment in GD cases diagnosed according to IADPSG criteria. It was observed that perinatal complications decreased from 4% to 1% in the study of Crowther et al. for randomized treatment activity on control group and the cases diagnosed with 75-g OGTT during 24–28 weeks. It was found that glucose control, diet and treatment program with insulin in required cases decreased perinatal morbidity significantly.[48] A similar randomized study was conducted by Landon et al. on a milder case group in 2009.[77] In that study, 50-g and 100-g glucose tests were used during 24–31 weeks of gestation on pregnant group who had abnormal values in tests but the level of preprandial BG was below 95 g. While perinatal losses (no perinatal death case) and severe newborn complications did not decrease with the treatment program applied in this study, a particular improvement was observed in the rates of birth weight, shoulder dystocia, cesarean and preeclampsia. Finding treatment activity even in mild cases with this study shows that glucose level and perinatal outcomes are directly associated even without a particular threshold value of HAPO study.[75] While the rates of cases diagnosed with GD increased twice by using 75-g and single value seem as an advantage, they seem as an advantage assessing the results of Landon et al.'s study.[77]

The direct association between perinatal outcomes and glucose level found in HAPO study (also in low glucose level) show the significance and efficiency of diet-exercise program. In this sense, applying 75-g and single value OGTT to all pregnant women doubles the rates of gestational diabetes but it also helps to apply

diet-exercise program to pregnant women and therefore to improve perinatal outcomes. Although its activity on short-term outcomes was revealed by the studies published by Crowther et al.[48] and Landon et al.,[77] there has been no study showing its activity on long-term outcomes. It will become clearer with further studies to be performed on the activity of this new diagnosis and treatment approach.

What Should We Recommend to Our Patients in Terms of Glucose Test?

As Perinatal Medicine Foundation and Turkish Perinatology Society, we have tried to establish a screening model for GD screening in our country within the perspective of evidence-based medicine. In Turkey, single-step 75-g diagnostic test seems more appropriate in terms of costs and patient compliance. Considering GD complications in particular, diagnosing under the light of our current information in order to protect fetus and mother from these complications is an evidence-based and scientific approach.

Studies on this Subject in Turkey

It was shown in a study investigating the effects of high pregestational maternal body mass index on gestational outcomes that pregestational BMI is related with more operative delivery and more neonatal problems.[78] GD prevalence was found as 21.1% in the study of Göymen et al.[79] It was claimed in the same study that there was no different in terms of GD rates when two-step or single-step screening is performed.[79] In a study investigating maternal serum leptin and malondialdehyde (MDA) levels in GD diagnosis and screening, it was reported that leptin, MDA and HbA1c levels increased significantly in GD cases, but the findings found was increasing the specificity of the tests performed during the GD screening.[80] In another study comparing maternal serum adiponectin and leptin measurements in GD diagnosis and screening, it was shown that adiponectin was more sensitive but had equal specificity in the group which underwent 75-g OGTT. Adiponectin was found significantly low in the group which underwent two-step screening.[81]

In a study evaluating 50-g screening and 100-g OGTT results of 690 pregnant women in terms of fetal macrosomia, it was argued that the patients with 50-g screening result over 140 mg/dl should be followed up closely in terms of fetal macrosomia like the patients with gestational diabetes even though their 100-g OGTT results are not positive.[82] In another study investigating the etiological factors in macrosomic fetuses, maternal age being above 35, high parity, high average of maternal height, weight gained during pregnancy being over 12 kg, high level of HbA1c, presence of polyhydramnios in current pregnancy and the medical history with macrosomic infant were considered as the factors increasing macrosomia risk in fetus.[83]

Type 1 / Type 2 Diabetes During Pregnancy

Diabetes is the disorder of carbohydrate metabolism affecting life considerably. It is a chronic disease leading long-term complications such as retinopathy, nephropathy and vascular diseases. It is seen in 2–5% of women in England. While 5% of this group is Type 2 DM, Type 1 DM is 7.5% and gestational diabetes is 87.5%. It is known that the rates of Type 1 and Type 2 diabetes gradually increase. Type 2 diabetes is frequently seen in Africa, Caribbean, South Asia, Middle East and China in particular.[6–8]

Miscarriage, preeclampsia and preterm delivery are seen frequently in diabetic pregnant women (Type 1 and Type 2). Besides, it should be remembered that retinopathy may get worse during pregnancy. Postpartum compliance problems such as stillbirth, congenital anomalies, macrosomia, birth trauma, perinatal mortality and hypoglycemia are seen more frequently.[22,23,31]

One of the first steps of making a successful follow-up in diabetic patients is to establish a good communication between healthcare professionals and patient. It is useful to provide detailed information on diabetes and pregnancy as well as delivering this information to patient in written. In this way, patient has a referring source when required.

Perinatal Medicine Foundation and Turkish Perinatology Society emphasize and recommend that the practices listed in **Table 4** are significant to obtain good perinatal outcomes in cases with overt diabetes and pregnancy (**Recommendations 1–7**).

Conflicts of Interest: No conflicts declared.

Table 4. Pregnancy and diabetes management.

Before pregnancy

- Patient should be informed about the importance of regulating glucose level well before pregnancy and also maintaining this level after pregnancy. In this way, the awareness that it is possible to prevent miscarriage, congenital malformation, stillbirth and newborn death should be raised.
  - Significance of diet, weight and exercise
  - Hypoglycemia developing during pregnancy
  - How nausea-vomiting during pregnancy may affect glucose control
  - How the condition of large for gestational age may increase birth trauma, labor induction and cesarean possibilities
  - How it is important to manage the condition of diabetic retinopathy before (treating if necessary) and during pregnancy
  - The importance of maintaining glucose level well during labor in order to prevent newborn hypoglycemia and providing early lactation of infant after birth
  - Conditions which may develop and require special or intensive care in infant after birth even temporarily.
- It should be informed in detail to such patients beginning from adolescence period that an unplanned pregnancy would be an undesired condition and it is very significant to conduct a well planned birth control and if it will be discontinued, to refer to doctor and make a pregestational plan..
- Diabetic patients planning pregnancy should be informed that:
  - Risks associated with diabetes during pregnancy is also associated with diabetes period
  - It is important to conduct conception until a well glucose control (HbA1c being below 6.1%) is provided
  - Glucose level targets, glucose monitoring, treatment options if necessary, and treatment options for problems associated with diabetes and pregnancy should be discussed
  - A closer cooperation is required during pregnancy and management plans such as emergency cases should be discussed in details.
  - Diet should be arranged for those planning to get pregnant
  - Weight loss program should be applied and informed about its significance for those planning to get pregnant and have BMI above 27
  - It is important to have 5 mg/day folic acid certainly by those planning to get pregnant in order to decrease the risk for neural tube defect
  - It is very important to do glucose measurements by themselves and they should be recorded by times.
  - Type 1 diabetics in particular have to do ketonuria check with sticks when their glucose levels elevate or when they do not feel well.

Reliability of diabetic drugs during pregnancy

- They should be informed that metformin used alone or as a support for insulin is an effective drug to get glucose levels. Other diabetic drugs should be discontinued before pregnancy and insulin should be used instead.
- It should be known that it was not shown in clinical studies that rapid-acting insulin analogues (aspart or lispro) used during pregnancy have negative effects on fetus or newborn.
- It should be stated to those undergoing insulin treatment or planning to get pregnant that there is insufficient data on the use of long-acting insulin analogues during pregnancy and therefore NPH insulin has been still an option preferred.

Treatment reliability of diabetic complications during pregnancy

- ACE inhibitors and angiotensin-2 receptor antagonists should be discontinued before pregnancy or they should be discontinued as soon as possible when pregnancy is detected. Instead, other alternative treatments should be performed.
- Statins should be discontinued as soon as possible when pregnancy is detected.

Retina evaluation before pregnancy

- Diabetic patients are absolutely required to have retina examination before pregnancy (if it is not performed within last 6 months).
- It is useful to perform this examination first by drop and then digital imaging

Renal examination before pregnancy

- It is significant to examine kidneys including microalbuminuria before discontinuing birth control. If creatinine is ≥120 or GFR is below 45, it should be re-evaluated after nephrology consultation.

Gestational follow-up

- Where possible, preprandial glucose level should be kept about 65–95 mg/dl and 1-hour glucose below 140 mg/dl, and importance of these levels should be explained.
- Patients with overt diabetes using insulin should be informed about the possibility of hypoglycemia attacks during first trimester in particular and the precautions.
- The cases whose glucose levels cannot be managed despite insulin use should be explained that using insulin pump is another method.
- Conditions where diabetic ketoacidosis is in question should be evaluated in hospital immediately and they should be put under care.
- It should be explained that diabetic retinopathy does not inhibit vaginal labor.
- The necessity of performing fetal cardiac examination during 13–14 weeks and also 18–22 weeks of gestation should be explained to all diabetic pregnant women.
- Unless there is fetal growth restriction, it is not necessary to do fetal well-being test routinely in diabetic pregnant women before 38 weeks of gestation.
- It should be explained to pregnant women with overt diabetes that they should visit for diabetes control with 1–2 weeks of interval.

Gestational follow-up

- First examination: Explaining the importance of and teaching glucose control, detailed anamnesis check for diabetes, drugs used, retina/kidney assessment
- Evaluating pregnancy at 7–9 weeks of gestation
- 13–14 weeks of fetal anatomy and fetal ECHO examination, diabetes and gestational interactions, delivery and lactation and newborn information
- Reevaluating if retinopathy/nephropathy is found
- Fetal anatomy and fetal ECHO examination at 20–22 weeks of gestation

Table 4. *[continued]* Pregnancy and diabetes management.

- Fetal development and amniotic fluid examination at 28 weeks of gestation, re-check if retinopathy/nephropathy is not detected in the first examination
- Fetal development and amniotic fluid check at 32 weeks of gestation
- Informing about fetal growth and amniotic fluid examination at 36 weeks of gestation, delivery timing-method and delivery management, analgesia/anesthesia, labor and then hypoglycemia management, infant care after delivery, lactation and its effect on glucose control, and conception
- Fetal well-being tests in pregnant woman with approaching delivery at 38 weeks and inducting labor or planning cesarean if necessary
- Fetal well-being tests at 39 weeks of gestation
- Fetal well-being tests at 40 weeks of gestation
- Fetal well-being tests at 41 weeks of gestation

Preterm labor

- Checking if diabetes constitutes contraindication for the administration of steroid or tocolyis (without using beta mimetics) if necessary
- Additional insulin will be required if steroid is administered, and glucose check should be performed more strictly

Timing and management of delivery

- In cases with normal fetal growth, delivery can be done by labor induction after 38 weeks of gestation and if necessary, cesarean can be planned
- If fetal macrosomia is in question, pregnant woman should be informed about the risks of vaginal delivery, labor induction and cesarean.
- In diabetic pregnant women, it would be beneficial to carry out evaluation and inform in terms of anesthesia in third trimester.
- If general anesthesia is applied, it should be known that glucose check is required every 30 minutes and it should be monitored until the effect of anesthesia diminish after delivery.

Managing labor

- Capillary glucose level should be checked every hour during labor and it should be kept at 75–125 mg/dl.
- Applying dextrose infusion as well as insulin as of the onset of labor
- If glucose level cannot be maintained at 75–125 mg/dl also in other cases, applying insulin together with dextrose infusion

Newborn management

- Diabetic pregnant women should deliver in a hospital capable of newborn resuscitation for 24 hours.
- Babies of diabetic mothers should be kept near their mothers. If any clinical complication or abnormal finding develops, then they should be monitored under special or intensive care conditions.
- Glucose control of the infants of diabetic mothers should be performed every 2–4 hours routinely and if there is any clinical finding, they should be controlled for polycythemia, hyperbilirubinemia, hypocalcemia and hypomagnesemia.
- If there is any cardiomyopathy finding including congenital cardiac anomaly or murmur, fetal ECHO should be carried out.
- Infants of diabetic mothers with following findings should be monitored in newborn intensive care units:
  - Hypoglycemia with clinical finding
  - Respiratory distress
  - Cardiomyopathy or cardiac failure due to congenital cardiac anomaly
  - Newborn encephalopathy
  - Polycythemia finding (need for partial blood exchange)
  - Intravenous fluid need
  - Need for gavage
  - Need for intense phototherapy and bilirubin control
  - Those born before 34 weeks
- Each obstetrics clinic should have and provide written information form for preventing, identifying and managing newborn hypoglycemia.
- Despite all kinds of efforts, if blood glucose level decreases below 36 mg in two consecutive measurements and if there is any abnormal clinical finding, gavage or intravenous dextrose application should be performed.
- If clinical finding of hypoglycemia is observed, glucose control should be performed immediately and dextrose should be rapidly administered intravenously.
- Newborns of diabetic mothers should be fed right after delivery (within 30 min.) and then every 2–3 hours.
- Those with Type 2 diabetes may continue using metformin but other drugs should not be used during lactation.
- The drugs for diabetic complications discontinued before and during pregnancy should be continued.

Effects of lactation on glucose control

- Those with overt diabetes should decrease insulin doses right after delivery and they should be managed with frequent glucose control until the optimum level is obtained.
- Those with overt diabetes and using insulin should be informed that hypoglycemia risk will increase after delivery and they should keep available food or snack as they may be required before and after lactation.
- If those with gestational diabetes are using drug, they should discontinue their treatment right after delivery.

Postpartum follow-up and information

- After delivery, those with overt diabetes should be referred to the clinic that they are followed up.
- The glucose levels of puerperants with gestational diabetes should be checked before discharging.
- Those with gestational diabetes should be warned and informed about the risk for developing hypoglycemia.
- Those with gestational diabetes should be checked for weight during postpartum period, diet-exercise applications should be maintained and their preprandial glucose levels should be checked at 6 weeks (not OGTT).
- Those with gestational diabetes should be warned and informed that they may be diabetic later. They should undergo preprandial blood glucose check or OGTT in advance when they plan pregnancy.

Recommendation 1

Informing each pregnant woman about pregnancy and diabetes

- In the first visit, they should be informed in detail about pregnancy process and this should be provided also in written. Gestational diabetes should certainly be explained as well as other gestational problems. For that purpose, the matters below should absolutely be discussed with pregnant woman, and;
- If the diagnosis of gestational diabetes is established, glucose level can be taken under control with diet and exercise in many cases,
- If diet and exercise are insufficient, 10–20% of cases may require taking insulin or tablets,
- More frequent follow-up and procedures may be required during pregnancy and delivery in those established with the diagnosis of gestational diabetes,
- If gestational diabetes cannot be detected, it should be informed that the risk for birth complication such as shoulder dystocia can be decreased.

Recommendation 2

Recommendations for gestational diabetes diagnosis

- If there are risk factors in the first prenatal visit, OGTT should be performed with 75-g glucose.
- If there is no risk factor, OGTT should be performed with 75-g glucose at 24–28 weeks of gestation.
- At postpartum 6–12 weeks, patients should be screened for diabetes by using diagnosis criteria in those non-pregnant women with OGTT.
- Women with gestational diabetes history should be screened for diabetes through entire lifetime at least once every 3 years.
- Changing life-style should be recommended for those with gestational diabetes history in order to prevent diabetes.

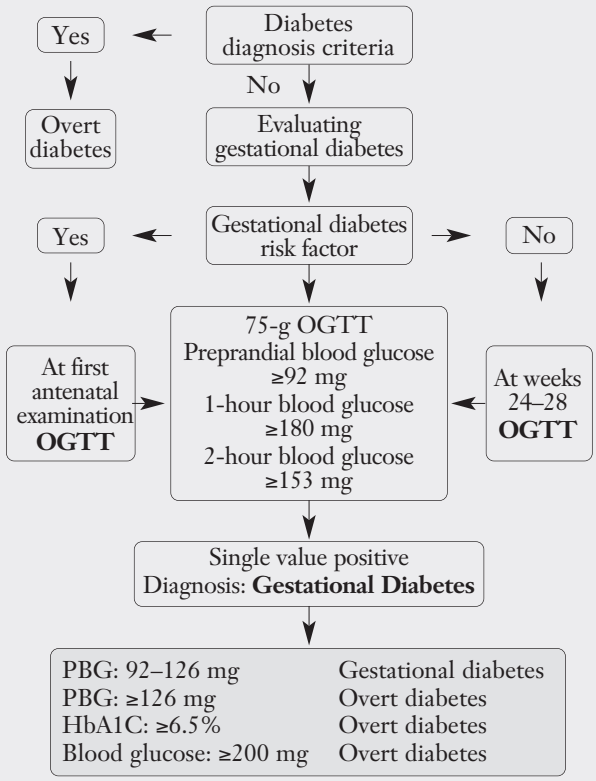
Recommendation 3

Risk factors for gestational diabetes

- GD presence in previous pregnancy
- Pregestational glucose intolerance diagnosis
- T2DM history in the family (especially in first degree relatives)
- Macrosomia and polyhydramnios history in previous pregnancy
- Mother gaining too much weight in previous pregnancy (>20 kg)
- Preprandial blood glucose >95 mg/dl and presence of glucosuria
- Overweight (BMI >25 kg/m^2)
- Advanced age (>25-year-old)
- Polycystic ovary syndrome

Recommendation 4

Diagnosis in gestational diabetes



Recommendation 5

Detailed information and education stated below should be provided to pregnant women established with gestational diabetes on diet-exercise-medical treatment.

- Recommending GD pregnant women to take food with low glucose index and to prefer food rich in protein and unsaturated fatty acid and fish
- Pregnant women with gestational diabetes and BMI over 27 to have a diet not exceeding daily 25 kcal/kg/day and 1750 calories for a pregnant woman who is 70 kg and to do a daily exercise program for approx. 30 minutes (morning–evening if possible)
- To undergo insulin or tablet treatment in cases whose glucose level cannot be maintained within 1–2 weeks despite diet and exercise,
- If it is found in fetal examinations that abdominal circumference is over 70 percentile, insulin or oral treatment may be required
- Treatment options with insulin (crystallized insulin or rapid-acting insulin analogues – aspart or lispro) and/or drugs such as metformin and glyburide

Recommendation 6

Follow-up during pregnancy

- ***Evaluating blood glucose levels:*** Weekly preprandial and postprandial 1-hour regular blood glucose follow-up, monthly HbA1C measurement
- ***Assessment of complications:*** Fundus examination at first trimester, follow-up at every trimester if necessary, follow-up of blood pressure and urinary albumin and creatinine at every visit. Consultation with specialists from related fields in case of any complication.
- ***Assessing biochemical parameters:*** Analysis of thyroid functions, renal functions and urine, lipid profile, examination of hepatic functions (at the beginning, and according to the condition later), urinary albumin follow-up every visit.
- ***Weight follow-up*** (weekly) and fetal growth follow-up (with 2–4 weeks of interval)
- ***Training:*** Blood glucose, hypoglycemia treatment and insulin administration training should be repeated every trimester
- ***Feeding:*** Daily 300 kcal is added in second and third trimesters to general calorie calculation.
- ***Fetal development and amniotic fluid*** should be monitored, and anomaly screening and fetal cardiac anomalies should be investigated in Type 1 diabetes cases in particular.

Follow-up criteria for gestational diabetes

Follow-up during pregnancy

- Evaluating glucose regulation: Preprandial and postprandial 1-hour blood glucose (a few times a week), HbA1C (every trimester).
- Following up blood pressure and urinary albumin (every visit)
- Weight follow-up (weekly) and fetal growth follow-up (with 2–4 weeks of interval)
- Evaluating biochemical parameters: Thyroid functions, renal functions and urinalysis, lipid levels, hepatic functions etc. (in the beginning, then according to patient)
- Training is necessary to complete delivery successfully.

Postpartum follow-up

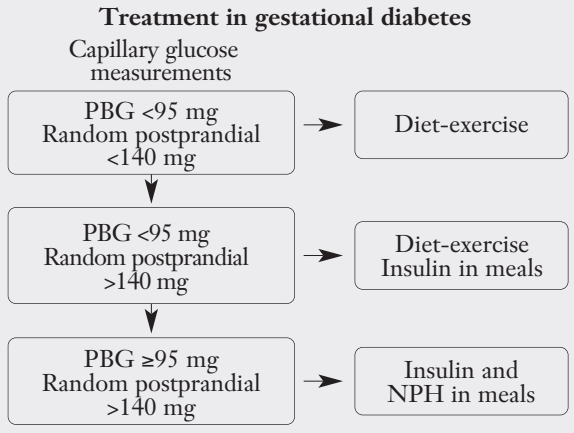
At hospital

- Measurement of preprandial and postprandial maternal 1-hour blood glucose
- Newborn follow-up (within first 4 hours after birth, long-term if hypoglycemia is present)

At home

- Measurement of preprandial and postprandial 1-hour blood glucose (until first postpartum visit)
- If follow-up results are normal in terms of diabetes during 3–6 months, evaluation 1 year later in the beginning and once every 3 years for the lifetime
- Significance of diet and exercise and lifestyle.

Recommendation 7



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