

## Guideline on Pregnancy and Diabetes by the Society of Specialists in Perinatology (PUDER), Turkey

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**ABSTRACT** Diabetes mellitus (DM) is the most common endocrinologic problem in pregnancy. In Turkey, the reported prevalence is between 1.9-27.9%, with an average of 7.7%. While some of these cases are pregestational diabetes (PGDM), about 90% are detected during the pregnancy for the first time and diagnosed as gestational diabetes (GDM). Diabetes in pregnancy confers serious risks regarding the fetus, newborn and the mother. Therefore, we offer GDM screening for all pregnant women preferentially between 24-28 weeks of gestation. Either one-step 75-g oral glucose tolerance test (OGTT) or two-step 50-g glucose challenge test and 100-g OGTT may be used for the screening and diagnosis. In pregnancies with high-risk for DM, screening should be performed earlier, if possible, in the first antenatal visit. When GDM is diagnosed, maternal glycemic control is tried to be achieved by diet and exercise program, and if necessary, by using insulin. The use of metformin or glyburide in pregnancy is also possible. In women with the diagnosis of DM before pregnancy, preconceptional control of plasma glucose levels is of utmost importance in order to prevent adverse pregnancy outcomes. In pregnancies with GDM regulated by diet and exercise, pregnancy follow-up may be performed as in the low risk group without any pregnancy complications. If maternal or fetal distress is not observed, delivery is planned between 39+0 -40+6 weeks. Although caesarean section is recommended when estimated fetal weight is 4500 g or more, the mode of delivery may be decided more appropriately on a case-by-case basis.

**Keywords:** Pregnancy; diabetes, gestational; diabetes mellitus

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## I- INTRODUCTION AND OVERVIEW

Diabetes mellitus (DM) is the most common endocrinologic problem in pregnancy. One to fourteen percent of pregnant women, with an average of 4-5%, suffer from variable degrees of glucose intolerance.<sup>1-3</sup> In Turkey, the reported prevalence is between 1.9-27.9%, with an average of 7.7%.<sup>4-6</sup> While some of these cases are pregestational diabetes (PGDM), about 90% are detected during the gestational period for the first time and diagnosed as gestational diabetes (GDM).<sup>3</sup> Maternal hyperglycemia and fetal hyperinsulinemia developing secondary to this, confer serious risks regarding the fetus, newborn and the mother (Table 1 and Table 2). These risks are more likely in PGDM.

Women with Type I or Type II PGDM must be evaluated preconceptionally for the control of plasma glucose levels and especially for the presence of chronic hypertension (CHT), coronary heart disease (CHD), nephropathy and proliferative retinopathy. Twenty-five percent of the cases with proliferative retinopathy may progress during pregnancy, particularly if there is co-existing CHT.<sup>7</sup> Moreover, the cases with diabetic nephropathy with serum creatinine levels over 1.5 mg/dL and with more than 3 g of proteinuria per day, are under the risk of renal insufficiency during pregnancy.<sup>7</sup> Preeclampsia may develop in 40-50% of women with nephropathy.<sup>8</sup> On the other hand, in diabetic women with CHD, pregnancy poses high risk as it may induce acute myocardial infarction and thus may result in morbidities and mortality.<sup>7</sup>

With proper preconceptional plasma glucose control and HbA1c levels of <6.5%, fetal anomaly risk will decrease significantly and will be similar to the risk in the healthy population.<sup>9</sup> In women treated with anti-diabetic drugs, switching to insulin, metformin or glyburide is necessary when pregnancy is planned or diagnosed. Periconceptional folic acid, at least 400 µg/day, should be offered ideally 8 weeks before the conception, and continued during the first 6 weeks (preferentially 12 weeks) of gestation.

**TABLE 1:** Pregnancy and diabetes-maternal risks.

- Spontaneous abortion
- Gestational hypertension (GHT) / preeclampsia (PE)
- Infections
- Dystocia
- Operative birth
- Postpartum hemorrhage
- Recurrence in future pregnancies
- Long term risks (overt diabetes, metabolic syndrome)

**TABLE 2:** Pregnancy and diabetes-fetal and neonatal risks.

- Congenital anomalies
- Intrauterine exitus
- Polyhydramnios
- Preterm birth
- Large for gestational age (LGA) (birthweight >90 <sup>th</sup> percentile with respect to the gestational age)
- Macrosomia (Birthweight ≥ 4000 g)
- Shoulder dystocia
- Intrauterine growth restriction (IUGR)
- Small for gestational age (SGA) (birthweight <10 <sup>th</sup> percentile with respect to the gestational age)
- Respiratory distress syndrome
- Neonatal hypoglycemia
- Neonatal hypocalcemia, hypomagnesemia
- Neonatal convulsions
- Neonatal polycythemia, hyperbilirubinemia
- Hypertrophic cardiomyopathy
- Childhood diabetes, obesity

## II- SCREENING AND DIAGNOSTIC TESTS FOR GESTATIONAL DIABETES

The effects of diabetogenic hormones become more prominent in the second half of pregnancy. All pregnant women should be offered GDM screening after 24 weeks of gestation, favorably between 24-28 weeks. Diagnosis and treatment of diabetes in pregnancy will significantly decrease the risks in the mother, fetus and neonate.<sup>10</sup> Screening may be performed either with one-step 75-g oral glucose tolerance test (OGTT) or two-step 50-g glucose challenge test (GCT) and 100-g OGTT, according to the clini-

cal circumstances or the preference of the clinician (Table 3 and Table 4).

When there is only one abnormal plasma glucose value in 100-g OGTT, although the case is not diagnosed as GDM, close surveillance of fetal growth and amniotic fluid volume, and if necessary, diet and exercise program for plasma glucose regulation, are recommended. The repetition of the test may clarify the diagnosis.

When randomly performed in pregnant women, either of the following values will indicate overt DM:

<b>TABLE 3:</b> One-step approach for gestational diabetes screening.
75 g oral glucose tolerance test (OGTT):
- Check fasting plasma glucose (FPG) level following at least 8 hours of fasting,
- Administer 75 g of glucose solution orally,
- Check plasma glucose levels after 1 hour and 2 hours,
- The values <92/180/153 mg/dL are considered to be normal for fasting/1 hour/ 2 hour plasma glucose levels, respectively.
- At least one abnormal value over the cut-offs confirms the diagnosis of GDM.

<b>TABLE 4:</b> Two-step approach for gestational diabetes screening.
50 g oral glucose challenge test (GCT):
- Administer 50 g of glucose solution orally in either fasting or postprandial status,
- Check plasma glucose level after 1 hour,
- <140 mg/dL is normal.
- If the result is ≥ 180 mg/dL, GDM is readily diagnosed.
- If the result is ≥ 140 but <180 mg/dL, 100 g OGTT is performed as the second step.
100 g oral glucose tolerance test (OGTT):
- Measure fasting plasma glucose (FPG) level following at least 8 hours of fasting,
- Administer 100 g of glucose solution orally,
- Measure plasma glucose levels after 1, 2, and 3 hours following administration,
- The values <95/180/155/140 mg/dL are considered to be normal for fasting/1 hour/2 hour/3 hour plasma glucose levels, respectively. (Carpenter&Causton criteria)
- GDM is diagnosed when two or more values are abnormal.

<b>TABLE 5:</b> Women with high-risk for DM.
DM in first-degree relatives
Obesity (body mass index ≥30 kg/m <sup>2</sup> )
Polycystic ovarian syndrome
Poor obstetric history (fetal anomalies/recurrent miscarriage/intrauterine fetal demise)
Macrosomia in previous pregnancies (neonatal weight ≥4000 g)
GDM in previous pregnancies

- Fasting plasma glucose (FPG) ≥126 mg/dL (7 mmol/L)
- Random plasma glucose ≥200 mg/dL (11.1 mmol/L)
- HbA1c ≥6.5%

If the FPG is ≥92 mg/dL in the first trimester of pregnancy, the case is considered as GDM and antenatal surveillance is performed accordingly.

In pregnancies with high-risk for DM (Table 5), screening tests should be performed before 24 weeks of gestation, if possible, in the first antenatal visit. Even when the results appear to be normal in early gestation, screening tests should be repeated at 24-28 weeks in this high-risk group.

### III- PRENATAL CARE IN DIABETIC PREGNANCIES

#### A- PRENATAL CARE IN PREGESTATIONAL DIABETES

##### i. Preconceptional Care

■ Plasma glucose regulation: Plasma glucose levels should be checked; the HbA1c level must be <6.5%. In patients treated with anti-diabetic drugs, switching preferably to insulin or to metformin or glyburide is recommended.

■ Initial evaluation of possible vascular complications:

- Hypertension
- Diabetic retinopathy - particularly proliferative retinopathy (ophthalmologic examination)
- Diabetic nephropathy (measuring proteinuria and creatinine clearance in 24-hour urine)
- Coronary heart disease (CHD)

- Thyroid function tests (TFT) (hypothyroidism occurs in 40% of the patients with type I DM)

- Folic acid should be administered at a minimum dose of 400 µg/day.

## ii. First Trimester

- Gestational age should be confirmed by early obstetric ultrasonography (USG).

- Endocrinology, Ophthalmology, Nephrology, and Cardiology consultations: Ophthalmologic examination must be performed at each trimester, and postpartum follow-up is also necessary for at least 1 year.

- Laboratory tests:

- HbA1c

- TFT

- Measurement of proteinuria and creatinine clearance in 24-hour urine

- Electrocardiography (ECG)

- Urine culture and other routine blood tests

- Plasma glucose regulation: Dietary treatment may be sufficient in some patients with PGDM. Insulin treatment must be initiated in patients treated with anti-diabetic drugs previously in the non-pregnant state. The use of metformin or glyburide in pregnancy is possible; however, first-line treatment is insulin. Maternal glycemic control is maintained either by multiple insulin injections or infusion pump and dietary restriction.

- Insulin dosage:

- 0.7-0.8 units/kg (current weight)/day in the first trimester

- 0.8-1 units/kg/day in the second trimester

- 0.9-1.2 units/kg/day in the third trimester

Fifty to sixty percent of total insulin dose should be provided by short-acting insulin and the remaining 40-50% by long-acting form. Short- or rapidly-acting insulin analogues (lispro or aspart) should be used just before meals (hypoglycemia should be considered as they act very quickly); the effect of regular insulin starts somewhat later. Long-acting insulin forms (Neutral Protamine Hagedorn-NPH, glargine, detemir) are used in the case of fasting and between meals.

- Capillary blood glucose measurement from fingertip is required to evaluate the glycemic control in the pregnant woman:

- Fasting,

- Preprandial measurements,

- One- or two-hour postprandial measurements,

- At bedtime.

- Diet:

- 30 kcal/kg (prepregnancy weight)/day in the first trimester,

- 24 kcal/kg/day in obese pregnant women (body mass index >30 kg/m<sup>2</sup>),

- 35 kcal/kg/day, starting from the second trimester on,

- Dietary content: 40-50% high fiber complex carbohydrates, 15-30% protein, 20-35% lipid (<10% saturated lipid),

- Three main meals and 2-4 snacks.

- Exercise: 30 minutes of moderate aerobic exercise is required for at least 5 days a week.

- Targets for plasma glucose levels:

- FPG ≤95 mg/dL

- Preprandial ≤100 mg/dL

- One-hour postprandial ≤140 mg/dL

- Two-hour postprandial ≤120 mg/dL

- Average plasma glucose 100 mg/dL

- HbA1c ≤ 6-6.5%

- It can be used together with plasma glucose measurements.

- Since it does not fully predict hypoglycemia/hyperglycemia attacks, it should be regarded as a secondary test in glycemic control.

- Due to the changes in erythrocyte cycle and glucose parameters during pregnancy, HbA1c levels should be followed-up more frequently (e.g., monthly).

- Folic acid started in the pregestational period should be used at least during the first 6 weeks of gestation (preferably 12 weeks) at a dose of minimum 400 µg/day.

■ Acetylsalicylic acid (ASA) 60-150 mg/day: It should be used for preeclampsia prophylaxis from the 12<sup>th</sup> week of gestation onwards, regardless of the presence of concomitant chronic hypertension. Although it is ideal to start ASA between 12-16 weeks, it can be offered until 28 weeks and continued until 37 weeks. It should preferably be ingested at night before sleep.

■ Pregnant women with PGDM should be evaluated by a perinatology specialist at 12 weeks of gestation. Measurement of the nuchal translucency (NT) at this week and first trimester fetal anatomic examination may allow for the detection of congenital anomalies earlier.

■ Fetal aneuploidy screening may be performed using the first trimester combined test (maternal age + NT measurement + PAPP-A and beta-hCG in maternal serum). However, the fact that PAPP-A levels may be lower in insulin-dependent diabetic pregnant women should be taken into account.

### iii. Second Trimester

■ If insulin is used, dose increase is usually required.

■ If fetal aneuploidy screening is to be performed by using triple or quadruple screening tests in insulin-dependent diabetic pregnancies, the laboratory must be informed about this diagnosis and a corrected result should be requested, since maternal serum alpha-feto protein (AFP) levels may be lower than those observed in uncomplicated pregnancies.

■ Screening for congenital anomalies: Anomaly screening must be performed by a perinatology specialist early between 16-18 weeks of gestation, and at the 22<sup>nd</sup> gestational week, anomaly scan must be performed once more together with fetal echocardiography.

■ Maternal serum AFP screening can be performed between 16-18 weeks of gestation, if there is no appropriate USG device for screening fetal anomaly. If the AFP MoM value (corrected AFP MoM value in patients with insulin-dependent diabetes) is greater than 2.5, the pregnant woman should be referred to a perinatology specialist.

### iv. Third Trimester

■ Insulin requirement increases throughout pregnancy, most apparently at 28-32 weeks of gestation.

■ Follow-up visits (obstetric follow-up) must be performed more frequently: at least every two weeks, more often after 36 weeks of gestation.

■ Assessment of fetal growth (obstetric USG): every two weeks, particularly after 32 weeks.

■ Antenatal surveillance tests for fetal well-being:

- Counting the fetal movements

- Non-stress test – NST (start performing after 32-34 weeks, twice a week)

- Biophysical profile (BPP)

- Doppler USG

BPP should be evaluated once or twice a week starting from 32-34 weeks. In pregnant women with vascular complications, tests for fetal well-being should be performed starting from the 28<sup>th</sup> week. Doppler examinations are important in pregnancies complicated by hypertension and/or intrauterine growth restriction (IUGR). Unexplained fetal death occurs more frequently after 35 weeks of gestation, especially in pregnancies with poor glycemic control.<sup>8,11</sup>

### B- PRENATAL CARE IN GESTATIONAL DIABETES

■ Diet: 30 kcal/kg (pre-pregnancy weight)/day in the first trimester, (24 kcal/kg/day in obese pregnant women); 35 kcal/kg/day from the second trimester onwards.

■ Exercise: Moderate aerobic exercise is required for 30 minutes, 5 days a week.

■ Plasma glucose levels are followed-up under diet and exercise (4 times a day): FPG and postprandial plasma glucose (after each of the 3 meals)

Optimal glycemic targets:

■ FPG  $\leq$ 95 mg/dL

■ One-hour postprandial plasma glucose <140 mg/dL or two-hour <120 mg/dL

There is no study showing the superiority of either one-hour or two-hour postprandial plasma glucose follow-ups.

■ If the plasma glucose levels are persistently high for 1-2 weeks despite the diet and exercise program:

■ FPG  $\geq 95$  mg/dL, and/or

■ One-hour postprandial plasma glucose  $\geq 140$  mg/dL or two-hour  $\geq 120$  mg/dL, pharmacological treatment is initiated.

■ Pharmacological treatment

- Insulin treatment: In women with GDM, insulin requirement is usually less compared to women with PGDM, and a total dose of 0.1-0.5 units/kg/day is usually adequate.

- Oral hypoglycemic agents have been under consideration in recent practice:

■ Metformin: initial dose: 500 mg/day, maximum dose: 2500 mg/day

■ Glyburide: initial dose: 2.5 mg/day, maximum dose: 20 mg/day

Indications of use of oral hypoglycemic agents:

- Pregnant women who cannot use insulin

- Pregnant women who refuse to use insulin

- When obstetricians consider themselves insufficient in terms of use of insulin.

Metformin use may be considered for those cases. There is not enough data for glyburide yet.

■ Follow-up of fetal growth and antenatal surveillance:

- Follow-up of cases with GDM regulated by diet, is not different from that of a normal pregnancy; if fetal movements are normal and there are no other complications, there is no indication for NST or BPP.

- In GDM cases who use insulin, fetal growth is evaluated by biometric measurements every two weeks, after 32 weeks of gestation. After 32-34 weeks, fetal well-being may be evaluated by NST twice a week. In addition, BPP may be performed once a week during follow-up. In cases of suspected vascular disease, poor glycemic control or IUGR, these tests should be started at 28-32 gestational weeks due to high risk for intrauterine fetal demise. Fetal movements felt by the mother should also be noticed ( $>10$  movements per 2 hours are expected). Unexplained intrauterine fetal deaths are usually ob-

served in fetuses which are large for gestational age (LGA) (estimated fetal weight (EFW)  $\geq 95^{\text{th}}$  percentile for the gestational age) and after 35 weeks of gestation.<sup>8,11</sup> Most of these are actually undiagnosed PGDM cases, just detected during pregnancy.

- Doppler examinations are important for pregnancies complicated by hypertension and/or IUGR.

#### IV- PLANNING THE DELIVERY IN DIABETIC PREGNANCIES

The following parameters should be taken into consideration while planning delivery in diabetic pregnancies:

1) Gestational age: It is determined according to the last menstrual period (LMP); however, if there is a difference of 5 days or more in ultrasound measurements in the first 8 weeks of pregnancy, or 7 days or more in 9-15 weeks, LMP should be corrected based on the ultrasound measurements.<sup>12</sup>

2) Type of diabetes and its regulation: In pregnancies with PGDM or GDM, maternal glycemic control is tried to be achieved by diet and exercise program, and if necessary, by using insulin or oral antidiabetic agents. Plasma glucose regulation is considered to be successful in patients with FBG  $<95$  mg/dL as well as one- and two-hour postprandial plasma glucose levels  $<140$  mg/dL and  $<120$  mg/dL respectively.

3) Presence of any maternal complications: Complications such as hyperglycemia/hypoglycemia, hypertension, proliferative retinopathy, nephropathy, CHD may be observed in diabetic pregnant women.

4) Presence of any fetal complications: In the ultrasonographic evaluation, when the EFW measurement is  $\geq 95^{\text{th}}$  percentile according to the gestational age, the fetus is considered to be a LGA fetus. LGA fetus, fetal abdominal circumference  $\geq 95^{\text{th}}$  percentile according to the gestational age, polyhydramnios, IUGR (EFW measurement  $<5^{\text{th}}$  percentile according to the gestational age), are among the fetal complications which can be observed in diabetic pregnancies.

#### TIMING OF DELIVERY

■ **GDM regulated by diet and exercise:** Pregnancy follow-up may be performed as in the low risk group without any pregnancy complications. If ma-

ternal or fetal distress is not observed, delivery is planned between 39+0-40+6 weeks.

■ **PGDM regulated by diet and exercise:** If maternal or fetal distress is not observed, delivery is planned between 39+0-39+6 weeks.

■ **GDM regulated by insulin/PGDM regulated by insulin:** Delivery is recommended between 38+0 - 39+6 weeks.

■ **Uncontrolled GDM/Uncontrolled PGDM or presence of maternal or fetal complications:** Delivery is recommended between 36+0-38+6 weeks. In the presence of maternal or fetal complications, particularly vasculopathy, nephropathy, hyperglycemia and history of stillbirth, delivery may be earlier if necessary.

#### MODE OF DELIVERY

In cases with GDM or PGDM, shoulder dystocia may be encountered during vaginal delivery due to atypical distribution of fetal adipose tissue independent of the birthweight. Shoulder dystocia is an unpredictable and unavoidable complication of delivery.

Ultrasonographically measured EFW has a high margin of error. Thus, although caesarean section is recommended when EFW is measured as 4500 g or more, the mode of delivery may be decided more appropriately on a case-by-case basis. If EFW is below 4500 g, the mode of delivery must be decided according to obstetric indications and maternal clinical pelvimetry.

In the presence of preterm labor, tocolytic agents and antenatal steroids which accelerate fetal lung maturation may be used with similar indications as in non-diabetic pregnancies. DM in pregnancy is not a contraindication for antenatal steroid administration. However, it should be known that antenatal steroid injections may impair plasma glucose regulation for up to 7 days and precautions should be taken for this situation.

During labor, plasma glucose level decreases due to labor itself as well as prolonged starvation. The recommendation is to make hourly measurements, and when necessary, to administer either solely 5% Dextrose solution or a neutralized 5% Dextrose solution (including  $\geq 5$  units of crystallized insulin/L) by intravenous infusion at 100 mL/h, in order to

maintain the plasma glucose levels within the range of 70-100 mg/dL.<sup>13</sup>

#### V- POSTPARTUM CARE AND RECOMMENDATIONS

■ In cases where insulin has been initially started during pregnancy, the dose may be reduced to half in the postpartum period and the therapy discontinued after 1-2 weeks; or it may be directly ceased depending on the plasma glucose levels.

■ In cases using insulin before pregnancy, the dose may be reduced to half on the first postpartum day. After the second day, it may be decreased to the pre-pregnancy dose.

■ In GDM or PGDM cases, any of the contraception methods can be used following the delivery when indicated.

■ In GDM cases regulated by diet, 75-g OGTT should be performed at postpartum 6-12 weeks. Overt DM is diagnosed when FPG is  $\geq 126$  mg/dL or 2<sup>nd</sup> hour plasma glucose is  $\geq 200$  mg/dL. If FPG is  $\geq 100$  to  $<126$  mg/dL, it is impaired FPG and if 2<sup>nd</sup> hour plasma glucose value is between  $\geq 140$  and  $<200$  mg/dL, it is evaluated as impaired glucose tolerance; hence the treatment is planned accordingly.<sup>14</sup>

■ Patients diagnosed as GDM in pregnancy have a risk of recurrence in subsequent pregnancies (48-66%), and a long-term risk of overt diabetes. Overt diabetes will be diagnosed in approximately 20% of the cases within 20 years.<sup>8</sup> These risks can be reduced by lifestyle changes, weight control, diet and exercise.

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#### Authorship Contributions

*All authors contributed equally while this study preparing.*

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