Gestational diabetes mellitus

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Abstract

Gestational diabetes mellitus (GDM) is defined as diabetes diagnosed during pregnancy that is not clearly overt diabetes. The current diagnostic criteria are as per recommendations of International Association of Diabetes in Pregnancy Study Groups (IADPSG) and is based on Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) study. Gestational diabetes has implications both for foetus and mother, and diagnosis and treatment of GDM improves pregnancy outcome. The first line of management of women with gestational diabetes consists of medical nutrition therapy (MNT) with adjunctive exercise. Oral hypoglycaemic agents (metformin, glyburide) have been found safe in pregnancy. Insulin is considered the standard for management of GDM. Self monitoring of blood glucose has been associated with a number of maternal and foetal benefits. Maintenance of euglycaemia is important in intra-partum period also to prevent neonatal hypoglycaemia. GDM is associated with increased long-term risks of diabetes, metabolic syndrome and increased cardiovascular disorders both in mother as well as in offspring. Women with apparent diabetes and impaired glucose tolerance should be identified by postpartum screening.

Keywords: Gestational diabetes, Pregnancy outcome, Insulin.

Definition

GDM is defined as diabetes diagnosed during pregnancy that is not clearly overt diabetes.1,2 It does not include women with type 1 or type 2 diabetes mellitus. The traditional definition of GDM "glucose tolerance with onset or first recognition in pregnancy" included women with unknown pre-existing diabetes; particularly type 2 diabetes mellitus (T2DM).1 A recent study in Pakistan had found a low prevalence (<1%) of GDM. In this study the mean BMI and age were 24 kg/m2 and 22 years respectively, and all women were primigravidae.3 Earlier study by Akhter et al. showed 3.3% prevalence among Pakistani women.4

Advances in Diagnosis

In 2011, American Diabetes Association (ADA) incorporated a new set of diagnostic criteria for diagnosis of GDM as per recommendations of IADPSG.1 The current criteria is based on oral glucose tolerance test (OGTT) cut-offs that identifies odds ratio of 1.75 for the risk of foetal macrosomia, neonatal adiposity, and foetal hyperinsulinaemia (all defined as >90th percentile) in HAPO study.5 Prior to 2011, ADA had endorsed the Carpenter and Coustan criteria, (derived from O’Sullivan criteria),which were validated in their ability to predict subsequent diabetes in the mother, whereas current criteria focus on maternal and perinatal complications of pregnancy.2,5

As per new ADA criteria, a woman is assigned a diagnosis of pre-existing diabetes if any of the following are present at first visit: fasting plasma glucose (FPG) ≥126 mg/dl; HbA1c ≥6.5%; random plasma glucose ≥200 mg/dl (confirmed by FPG or HbA1c). If FPG at first visit is <126 mg/dl but ≥92mg/dl, the woman is diagnosed to have GDM. The woman without pre-existing diabetes or GDM at first visit should undergo 75-g, 2-h OGTT at 24-28 weeks gestation. The diagnosis of GDM is made if any of the following plasma glucose values is met; FPG ≥92mg/dl; 1 h ≥180mg/dl or 2 h ≥153 mg/dl (Figure).6

Advances in Screening

There is continuing debate on screening based on risk factor assessment. The American College of Obstetricians and Gynaecologists (ACOG) recommends universal screening by 2 step approach. The first step is a 50-g, 1-h glucose challenge at 24-28 weeks. Values ≥130mg/dl or ≥140mg/dl are followed up with a 100-g, 3 hours OGTT. The ACOG has not yet adopted the IADPSG recommendations for diagnosis of GDM.7 A cost-effective strategy has been proposed by Diabetes in Pregnancy Study Group India (DIPSI). As per DIPSI, GDM is diagnosed if 2h plasma glucose value is ≥140mg/dl after a 75g oral glucose load irrespective of whether the woman is in fasting or non fasting state.8

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Look for glycaemic status at first visit of pregnant woman

- FPG > 126 mg/dl or HbA1C > 6.5% or Random plasma glucose ≥ 200 mg/dl (confirmed by FPG or HbA1c).
  - Overt Diabetes of pregnancy

- FPG < 126 mg/dl but ≥ 92 mg/dl
  - GDM

If no overt diabetes or GDM on investigation
- Perform 75-g OGTT at 24-28 weeks of gestation

Management

A. Antenatal
1. Medical nutrition therapy
2. Exercise
3. OHA’s (Glyburide and metformin safe in pregnancy) Only short term safety data is available
4. Insulin (Adequate safety data for glargine and glulisine is lacking, both are pregnancy category C drugs)

Aim is to achieve glycaemic goals
1. FPG ≤ 95 mg/dl
2. 1 h after meals < 140 mg/dl
3. 2 h after meals < 120 mg/dl

B. Peripartum
- The goals of intrapartum insulin management are to maintain normoglycaemia (BG 70-110 mg/dl) to optimize foetal tolerance of labour and prevent neonatal hypoglycaemia.

C. Postpartum
- Maintain lifestyle modification
- Postpartum screening at 6-12 weeks with non-pregnant 75-g OGTT
- If NGT: Repeat at 3 years
- If IGT or IFG: Repeat annually

The diagnosis of GDM is made if any of the following plasma glucose values is met;
1. FPG > 92 mg/dl
2. 1 h ≥ 180 mg/dl
3. 2 h ≥ 153 mg/dl

GDM: Gestational diabetes mellitus; OGTT: Oral glucose tolerance test; FPG: Fasting plasma glucose; NGT: Normal glucose tolerance; IGT: Impaired glucose tolerance; IFG: Impaired fasting glucose; OHA’s: Oral hypoglycaemic agents.

Figure: Flow diagram to approach to a woman during pregnancy for glycaemic status.
Complications of Gestational Diabetes Mellitus

Glucose is easily transferred across the placenta. Maternal hyperglycaemia leads to foetal hyperglycaemia, foetal hyperinsulinaemia and consequently to diabetic foetopathy. The growth promoting activity of insulin results in foetal macrosomia, which predisposes to shoulder dystocia. The ACOG recommends consideration of elective caesarean section to avoid shoulder dystocia, if the estimate of foetal weight is in the range of 4500 g.

Hyperinsulinaemia also makes such neonates prone to hypoglycaemia, due to sudden interruption of blood glucose support from mother after delivery. Other neonatal complications include hypocalcaemia, hyperbilirubinaemia, and plethora. The woman with undiagnosed, untreated GDM has high risk of pre-eclampsia and preterm labour, and her infant is more likely to develop respiratory distress syndrome and other problems of prematurity.

Advances in Treatment

The Australian Carbohydrate Intolerance Study in Pregnant Women and the Maternal-Foetal Medicine Units Network treatment of mild gestational diabetes clinical trials showed that diagnosis and treatment of GDM does improve pregnancy outcomes.

Lifestyle Modification

The first line of management of women with GDM consists of medical nutrition therapy (MNT) with adjunctive exercise for at least 30 minutes per day. ADA recommends diet that adequately meets the needs of the pregnant woman but restricts carbohydrates to 35-40% of daily calories. ADA also suggests 30-33% calorie restriction for obese women with GDM while advising a minimum 1800 calorie diet, to avoid ketosis.

Physical activity limited to 30 min/day is recommended for all individuals capable of participating. Advising GDM patients to walk briskly or to do arm exercises while seated in a chair for at least 10 minutes, timed 30 minutes after each meal accomplishes this goal.

Oral Hypoglycaemic Agents (OHAs)

Insulin is the gold standard for management of GDM, when lifestyle modification fails to achieve glycaemic targets. OHAs were avoided in pregnancy because of fear of neonatal hypoglycaemia and teratogenicity associated with placental transfer to the foetus. But, ease of administration, increased adherence, low cost, simple dosing, low risk of teratogenicity, and lack of adverse psychological impact and social stigma associated with insulin use, have resulted in increased use of metformin and glyburide in pregnancy. Metformin and glyburide are category B medications in pregnancy. A meta-analysis found no statistically significant difference in glycaemic control between OHAs (4 studies of glyburide, 2 studies of metformin) and insulin. The incidence of neonatal hypoglycaemia was slightly less and birth weight was also slightly lower with metformin as compared to insulin, and slightly high with glyburide as compared to insulin. There was no significant difference between the 2 treatment groups in the incidence of admission to NICU; neonatal respiratory distress; incidence of birth injuries; small for gestational age; preterm births; congenital anomalies; and intrauterine foetal death. The maternal hypoglycaemia rate was 8.8% in OHA group and 22.2% in the insulin group. Incidence of maternal hypertensive disorders was slightly higher in the insulin group (10.65% vs 8.16%). There was no significant difference in the caesarean section rate in the 2 treatment groups. The study that compared metformin with insulin found high (46.3%) conversion rates to insulin. The conversion rate from glyburide to insulin was 4%.

Metformin does cross the placenta, but being an insulin sensitizer, is less likely to cause severe neonatal hypoglycaemia. In vitro studies show minimal transfer of glyburide across the placenta. Glyburide is found to be safe to foetus at maternal doses up to 20mg/d.

The two drugs are not yet FDA approved for use in pregnancy. Long-term safety data on infants whose mothers were treated with these OHAs is lacking. One may, however, support the cautious use of metformin in pregnancy, with strict maternal and foetal surveillance, including regular monitoring for ketonuria.

Insulin

Insulin is the gold standard for the treatment of pregnant women, who have failed diet and lifestyle modifications. Insulin analogues have a more rapid onset of action than the regular insulin preparations and have a potential theoretical advantage in controlling the postprandial glucose excursions. Both aspart and lispro are pregnancy class B drugs. Insulin glulisine (Category C) has limited evidence of safe use in pregnancy. Recently published RCT comparing detemir with NPH insulin in TIDM in pregnancy has shown similar level of glycaemic control, hypoglycaemic episodes, and incidence of adverse
perinatal outcomes in 2 arms and has not raised any safety issue with detemir. At present detemir is category B and glargine is category C drug for use in pregnancy. Glargine has safety concerns with regard to its increased mitogenic potency, compared to human insulin.

**Self-monitoring of Blood Glucose (SMBG)**

SMBG has been associated with maternal and foetal benefits. SMBG four times per day in patients with diet-treated gestational diabetes, and six times per day in women with insulin-treated diabetes is advocated as per expert opinion. Blood glucose measurement performed in fasting, pre-meal, 1 hour after the start of each meal (postprandial glucose), and at bedtime improves the glycaemic control.

ADA recommended targets for home-monitored capillary glucose levels during pregnancy are FPG \(<\)95mg/dl; 1 h after meals \(<\)140mg/dl and 2 h after meals \(<\)120mg/dl.

**Peripartum Management**

The goal of intrapartum insulin management is to maintain euglycaemia (BG 70-110 mg/dl) to optimize foetal tolerance of labour and prevent neonatal hypoglycaemia. Women with GDM can be managed with lower doses of insulin during labour, because uterine contractions increase insulin sensitivity and reduce insulin needs. Metformin and glyburide use is safe during breastfeeding mothers. The mean infant exposure to metformin is less than 1% of the weight-normalized maternal dose. The safety data in this context is from studies with limited number, and safety of OHAs use during breastfeeding is not universally agreed upon. Hence, insulin prescription is a safer option.

**Impact on Long Term Maternal Health**

GDM is associated with increased long-term risks of diabetes, metabolic syndrome and cardiovascular disorders. While most cases of GDM resolve with delivery, these individuals are at 7 fold increase risk of developing T2DM subsequently. ADA recommends screening for diabetes at 6-12 weeks postpartum, every three years thereafter, but annually in women with prediabetes, using non-pregnant (OGTT) criteria. Women with a history of GDM found to have prediabetes should receive lifestyle interventions or metformin to prevent diabetes.

**Impact on Long Term Offspring Health**

Foetal exposure to a hyperglycaemic environment increases the risk of developing obesity, metabolic syndrome and T2DM in future. In Growing Up Today Study, which included examination of offspring (aged 9 to 14 years) of mothers with GDM, it was found to be associated with an increased risk of adolescent overweight.

**Conclusions**

GDM presents a window of opportunity to prevent diabetes and associated metabolic illness, not only in the mother, but also in the unborn generation. Active screening, diagnosis, lifestyle management, MNT, and drugs, if required, will help not only in improving short term maternal and foetal outcomes, but will also bring down the long term ill consequences.

The main goal during pregnancy should be not to miss any opportunity of screening a woman for overt or gestational diabetes (author’s personal opinion), and ensuring euglycaemia. Equally important, one should ensure that opportunities for postpartum screening and intervention are not missed. Postpartum screening should aim to identify women not only with apparent diabetes but also impaired glucose tolerance, so that diabetes can be delayed or prevented.

**References**