

Review Article

Diabetes in Pregnancy

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Abstract

Diabetes is one of the commonest medical complications of pregnancy. It could antedate pregnancy or be identified for the first time during pregnancy when it is termed Gestational diabetes mellitus (GDM). GDM is plagued by controversies right from screening, diagnosis and interventions. Identification of GDM is important as it impacts maternal health care during and after pregnancy. Following Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study and International Association of Diabetes and Pregnancy Study Groups (IADPSG) recommendations, a new screening and diagnostic criteria seems to be gaining consensus around the world. As India is fast catching up with China to become the diabetic capital of the world, thrust is now on universal early testing in our populations at the first prenatal visit. Diabetes in Pregnancy Study Group India (DIPSI) has also suggested cost effective method of screening in resource-challenged communities. GDM offers an excellent opportunity for primary prevention of Diabetes, as the mothers are at increased risk of future diabetes, predominantly type 2 diabetes, as are their children.

Key Words : Diabetes in Pregnancy, Gestational diabetes mellitus, Guidelines, Hyperglycemia and Adverse Pregnancy Outcomes

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Introduction

GDM is defined as glucose intolerance that is first recognized during pregnancy. The prevalence of GDM corresponds to the prevalence of IGT within a given population. It ranges from 1.4% to 2.8% in low risk populations to 6-10% in high risk populations^{1,2}. The prevalence is higher among Asian women compared to the whites (8.7% vs 3.9%). The so-called Asian Indian Phenotype refers to certain unique clinical and biochemical abnormalities in Indians which includes increased insulin resistance, higher waist circumference despite lower body mass index. This phenotype makes Indians more prone to diabetes. Maternal hyperglycemia mild or severe has an adverse impact on maternal health such as risk of operative deliveries, gestational hypertension and preeclampsia. Perinatal morbidities may include macrosomia, birth trauma, hypoglycemia, hyperbilirubinemia, polycythemia etc³. Women known to have diabetes must control their blood glucose (HbA_{1c} < 6.3%)⁴ before planning conception. The present review article shall focus more on defining GDM, its present day relevance, screening, and diagnostic criteria.

The Indian Scenario

India would be having the highest population of diabetes by 2025.⁵ The increased prevalence is attributed to improved life expectancy, urbanization, changing dietary habits, the obesity epidemic, and physical inactivity.⁶ Studies from various parts of India

reports prevalence of 6% to 18.8%. In a national survey for the prevalence of GDM we found 16.55% of pregnant women having 2-hour PPG 140mg/dl, which was closer to the prevalence of IGT in our country. (Urban > Rural).⁷ The obesity epidemic has compounded the problem. The prevalence of GDM in underweight (BMI-13-18.4) is 0.7%, normal weight (18.5-24.9) is 2.3%, overweight (25-29.9) is 4.8%, obese (30-34.9) is 5.5% and in extremely obese (35-64.9) is 11.5%.

Definition

In 2010, the IADPSG, an international consensus group with representatives from multiple organizations, recommended a change in the terminology.

In this, diabetes diagnosed during pregnancy is classified as overt or gestational. ADA endorsed this in 2011.^{8,9}

Overt diabetes: At the first antenatal visit, if a woman has a fasting plasma glucose (FPG) \geq 126mg/dl or HbA_{1c} \geq 6.5% or a random plasma glucose \geq 200 mg/dl.

Gestational diabetes: Women who have FPG \geq 92 mg/dl but <126 mg/dl at any gestational age GTT at 24-28 weeks –with at least one abnormal value: FPG \geq 92 mg/dl but < 126 mg/dl One hour \geq 180 mg/dl or two hour \geq 153mg/dl

Pathophysiology

Pregnancy is normally associated with progressive insulin resistance beginning from midpregnancy through to term. It arises from increased maternal adiposity and the placental hormones namely, human placental lactogen, placental growth hormone variant, cortisol, progesterone etc. This puts an added strain to the beta cells to compensate for the insulin resistance. Those who are unable to do so develop glucose intolerance. In women with GDM, these physiological changes are superimposed on underlying chronic insulin resistance and beta cell dysfunction. This also explains higher prevalence for GDM in women with polycystic ovarian syndrome.

Whom to screen?

The screening strategies that range from selective targeted screening of moderate to high risk individuals to universal screening depends on the prevalence of diabetes in that population (IADPSG). The relative risk of developing Gestational Diabetes Mellitus in Asian Indian women is 11.3 times compared to White women. This necessitates universal screening for gestational diabetes during pregnancy in India as recommended by DIPSI.¹⁰

In population with lower diabetes prevalence, timing of screening depends on the risk profile. Women at high risk are offered screening at first antenatal visit, moderate risk at 24-28 weeks. (ADA)

Low-risk status

- Age <25 years.
- Normal BMI.
- Member of an ethnic group with a low prevalence of gestational diabetes mellitus .
- No known diabetes in first-degree relatives .
- No history of IGT.
- No history of poor obstetric outcome

High risk status

- Age > 25 years
- Obese / overweight
- Strong family history of diabetes
- Previous h/o macrosomia/foetal loss
- Persistent glycosuria
- Past h/o IGT / GDM
- Ethnic group with higher prevalence of DM
- H/o polyhydramnios / stillbirths / congenital anomalies.

When and how to screen?

- 50 gm GCT without regard to the time since last meal
- If >140 mg/dl, 100 gm GTT to be offered. If 2 or more values are abnormal GDM is diagnosed.

	NDDG (1979)	CC (1982) ¹²
Fasting	> 105 mg/ dl,	> 95
1 hour	> 190 mg/dl,	> 180
2 hours	> 165 mg/dl,	> 155
3 hours	> 145 mg/dl.	> 140

NDDG :National Diabetes Data Group, CC: Carpenter and Coustan

The IADPSG recommends 75 gm two hour GTT and the thresholds are based on the HAPO study. The Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study¹¹ was a large multinational epidemiologic study, involving 25,505 pregnant women at 15 centers in nine countries. These women underwent 75-g oral glucose-tolerance testing at 24 to 32 weeks of gestation. This was designed to examine the effects of milder maternal hyperglycemia and adverse outcomes mentioned below. Multiple logistic regression was used to examine associations of GDM and obesity with outcomes.

It demonstrated that risk of adverse maternal, foetal, and neonatal outcomes continuously increased as a function of maternal glycemia at 24-28 weeks, even within ranges previously considered normal for pregnancy. For most complications, there was no threshold for risk.

75 gm GTT- FPG \geq 92, 1 hr \geq 180 , 2 hr \geq 153 mg/dl. Any one abnormal value defines GDM.

The lower cutoffs were determined by the average glucose values at which risk for

- Birth weight > 90th centile
- Cord C-peptide > 90th centile
- Percent body fat > 90th centile
- Preeclampsia Increased by 1.75- 2 times, compared to mean glucose values

Preterm delivery and need for Caesarean - section increased by 45%

By applying this new criteria, the incidence of GDM would go up to 17.8% because only one abnormal value, not two, is sufficient to make the diagnosis. The diabetic associations around the globe recognize the anticipated overdiagnosis and "medicalization" of pregnancies previously categorized as normal. There are few data from randomized clinical trials for being modest^{16,17} IADPSG - 2010 recommendations are endorsed in the ADA position statement in Jan 2011. ^{8,9}

Two discrete phases: The first is detection of women with overt diabetes not previously diagnosed or treated

outside pregnancy. Universal early testing in populations (with a high prevalence of type 2 diabetes) is recommended at the first prenatal visit. The second phase is a 75-g OGTT at 24-28 weeks gestation in all women not previously found to have overt diabetes or GDM.

DIPSI Recommendations: DIPSI has suggested a one step procedure with a 2 hour plasma glucose after a 75 gm glucose load without regard to time of the last meal. A 2 hr plasma glucose >140 mg/dl defines GDM, if it is 120-139 mg/dl it is termed Gestational glucose intolerance (GGI). If the test is normal, test repeated at 24-28 wk and then 32-34 wks.¹⁰

Maternal and Foetal complications in Pregestational and GDM

Maternal Complications include risk of abortions, chorioamnionitis, preeclampsia, postpartum bleed, higher rates of Cesarean section. In pregestational diabetes, there could be progression of diabetic nephropathy and retinopathy, higher insulin requirements and higher mortality if previously affected by CAD or cardiomyopathy. Foetal effects include congenital anomalies such as Transposition of great vessels, septal defects, hypoplastic LV, CNS anomalies like spina bifida, anencephaly, neural tube defects, caudal regression syndrome, genitourinary anomalies, anorectal atresia etc.

Other effects include macrosomia, foetal demise during the last 4-6 weeks.

Neonatal complications include respiratory distress, hypoglycemia, hypocalcemia, hyperbilirubinemia, polycythemia etc.

Preconceptional Care

All women with either Type 1 or 2 diabetes planning pregnancy must be counseled about the need to achieve a good glycemic control ($A_{1c} < 6.3\%$) to reduce the risk of congenital anomalies and spontaneous abortions.⁴ They must be screened for retinopathy and microalbuminuria before planning pregnancy. Eye testing is recommended in all the trimesters of pregnancy. They must be instructed to follow diet and regular exercises. Those on oral hypoglycemic agents, ACE inhibitors or ARBs, statins, fibrates or beta blockers need to change their medications.⁴ Pregnancy is risky for those with advanced nephropathy / retinopathy or CAD or severe hypertension. Starting an insulin regimen before conception allows women to become familiar with insulin self administration and dose adjustment.

Management

A multidisciplinary approach is required comprising obstetrician, diabetologist, diabetic educator, dietician and a pediatrician.

Target blood glucose levels : To maintain a mean plasma glucose level of 105-110 mg/dl for a favourable obstetrician, diabetologist, diabetic educator, dietician and a pediatrician.

Target blood glucose levels : To maintain a mean plasma glucose level of 105-110 mg/dl for a favourable foetal outcome, it is desirable to have fasting glucose <90 and 2 hour post prandial < 120mg/dl respectively. The recommendations are:

ADA (capillary glucose) –premeal ≤ 95 , 1hrPP ≤ 140 and 2hr PP ≤ 120 mg/dl

5th international workshop-premeal <96, 1hrPP<140 and 2 hrPP<130 mg/dl

A) Medical nutrition therapy (MNT)

Goals : To achieve normoglycemia, prevent ketosis and provide adequate weight gain. MNT is tried for two weeks.

- 3 meals and 3 snacks pattern, a bedtime snack must to prevent ketosis in fasting state
- Ideally split breakfast into two portions to avoid peaking of plasma glucose due to Dawn phenomenon
- Carbohydrates restricted to 40-45%. Carbohydrate counting to be practiced, low glycemic index foods to be chosen
- Underweight : 36-40 kcal/kg , 12.5-18 kg wt gain
- Ideal body weight: 30 kcal/kg , 11.5-16 kg
- Overweight : 24 kcal/kg , 7-11.5 kg
- Obese : 12-18 kcal/kg, 6 kg
- All must continue folate and iron and vitamin D as indicated.
- Recommended protein -1.1g/kg
- More than 90% patients can be managed with MNT(DIPAP)¹⁰

B) Physical activity

Planned physical activity of 30 minutes /day. One could do arm exercises /walk briskly for 10 minutes after each meal. Upper body exercises are always preferred.

C) Pharmacological therapy

Insulin: The safest therapeutic option in those failing MNT(category A). If the FPG>120 mg/dl or PP>199 mg/dl, insulin is initiated along with MNT.

Human insulins (both short and intermediate acting)can be given as a basal bolus regimen or as a premixed insulin(30/70 or 50/50).

Role of Insulin Analogs

Rapid using insulin analogs like Lispro and Aspart (both category B) can be considered if the postprandial glucose is not under control. Premixed analogs have also been found to be safe.

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Long acting analogs like Glargine (Category C) and Detemir (FDA category B) have also been approved. Women with pregestational diabetes require more insulin than those with GDM. If insulin requirement drops it could mean placental dysfunction or foetal jeopardy or increased glucose utilization by the macrosomic fetus.

Oral hypoglycemic agents

a) **Glibenclamide:** Of the sulphonylureas, this crosses the placenta the least (foetal concentration <1% of maternal levels). A randomized unblinded clinical trial on 404 GDM patients compared glyburide vs insulin. The OHAs was initiated after the 1st trimester. There was no difference in the perinatal outcomes¹³.

b) **Metformin:** More recent studies have found it to be safer, with no perinatal complications. Continuing metformin in women with PCOS after conception throughout pregnancy is being favoured by few studies. Those on metformin required lesser insulin and had lesser weight gain.¹⁴

Monitoring glycemic control

HbA_{1c} level tested in early pregnancy is helpful to differentiate between an overt diabetic and GDM. If the value is more than 6%, she is likely to have overt diabetes. HbA_{1c} as a tool in monitoring the glycemic control during pregnancy may serve as a prognostic value. It is not routinely recommended in the second and third trimesters of pregnancy. If HbA_{1c} level is used to monitor glucose control in pregnancy, the target level to be maintained is 5.3%, which corresponds to a fasting blood sugar level of 90 mg/dl and 2-h post-meal level of 120 mg/dl¹⁸.

Self monitoring of blood glucose (SMBG) is encouraged 4 times daily (fasting/1hr or 2hr PP) once a week. Postprandial monitoring is found to be superior to premeal monitoring – better HbA_{1c}, lower LGA and lower rate of Cesarean Section. The mothers also need to be taught self dose adjustment. Continuous glucose monitoring system (CGMS) may be required only in those cases where sugars are difficult to control.¹⁵

Foetal Surveillance: Ultrasound: baseline, 20 week anomaly scan, from 26 weeks onwards for growth and liquor volume.

- 3rd Trimester : Abdominal : Head Circumference Ratio checked.
- Maternal monitoring of foetal activity

The nonstress test (NST), Doppler umbilical artery velocimetry

Timing of delivery: before full term is not indicated unless for obstetric indication-(Pre eclampsia, IUGR), macrosomia and polyhydramnios.

Labour; Control maternal glucose levels during labour to prevent foetal hyperinsulinemia, acidosis and neonatal hypoglycemia

- <70 mg/dl – Dextrose Normal Saline (DNS) 100 ml/hr
- 90-120 mg/dl – Normal Saline (NS) 100ml/hr, CBG every 1-4 hourly intervals
- Regular Insulin given as infusion only if glucose >140 mg/dl.
- Post delivery keep patients on DNS

Neonatal management – Monitor for respiratory distress, check capillary glucose 1, 2 and 4 hrs after birth and after feeding. Early breast feeding is encouraged.

- Post partum period: Insulin sensitivity improves and insulin requirements drop.
- 75 gm OGTT offered 6-12 weeks post partum – if normal, it should be repeated after 6 month and annually. Women should be counseled about their future risk for diabetes.

Conclusions

Gestational diabetes offers a good opportunity for primary prevention of diabetes not only in the mother but also her offspring. A short term intensive care ensuring good glycemic control, good maternal nutrition and a normal birth weight of the baby gives a long term payoff in the prevention of obesity, impaired glucose tolerance and diabetes in the baby. This can be ensured only by a committed team of obstetrician, diabetologist and pediatrician.

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Let there be "blue" light!

Skin and soft tissue infections are the second most common infections encountered in clinical practice. Treatment of these is becoming more and more difficult due to emergence of antibiotic resistant strains. One enzyme in particular, NDM-1, makes some bacteria resistant to almost all antibiotics. Some researchers are apprehensive that the antibiotic era as we know of it may be coming to an end and we might be gazing down a dark tunnel. But a recent animal study done at Harvard Medical school hints at the presence of light at end of the tunnel and the colour of that light is blue. In that study the researchers used two groups of animals infected with *P. Aeruginosa*: one group was treated with blue light while the other acted as control. The animals treated with blue light recovered completely whereas 82% of animals died among the controls. The study has shown that the "blue" light can selectively eradicate *P. Aeruginosa* infection without damaging the skin. The results will be published in the March 2013 issue of *Antimicrobial Agents and Chemotherapy*.

- Dr. K. Ramesh Rao