Gestational Diabetes Mellitus – Guidelines*

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Abstract

The Diabetes In Pregnancy Study group India (DIPSI) is reporting practice guidelines for GDM in the Indian environment. Due to high prevalence, screening is essential for all Indian pregnant women. DIPSI recommends that as a pregnant woman walks into the antenatal clinic in the fasting state, she has to be given a 75g oral glucose load and at 2 hrs a venous blood sample is collected for estimating plasma glucose. This one step procedure of challenging women with 75 gm glucose and diagnosing GDM is simple, economical and feasible. Screening is recommended between 24 and 28 weeks of gestation and the diagnostic criteria of ADA are applicable. A team approach is ideal for managing women with GDM. The team would usually comprise an obstetrician, diabetes physician, a diabetes educator, dietitian, midwife and pediatrician. Intensive monitoring, diet and insulin is the corner stone of GDM management. Oral agents or analogues though used are still controversial. Until there is evidence to absolutely prove that ignoring maternal hyperglycemia when the fetal growth patterns appear normal on the ultrasonogram, it is prudent to achieve and maintain normoglycemia in every pregnancy complicated by gestational diabetes. The maternal health and fetal outcome depends upon the care by the committed team of diabetologists, obstetricians and neonatologists. A short term intensive care gives a long term pay off in the primary prevention of obesity, IGT and diabetes in the offspring, as the preventive medicine starts before birth. ©

INTRODUCTION

The maternal metabolic adaptation is to maintain the mean fasting plasma glucose of 74.5 ± 11 mg / dl and the post prandial peak of 108.7 ± 16.9mg / dl.[1] This fine tuning of glycemic level during pregnancy is possible due to the compensatory hyperinsulinaemia, as the normal pregnancy is characterized by insulin resistance. A pregnant woman who is not able to increase her insulin secretion to overcome the insulin resistance that occurs even during normal pregnancy develops gestational diabetes.

The metabolic goals of pregnancy are 1) in early pregnancy to develop anabolic stores to meet metabolic demands in late pregnancy and 2) in late pregnancy to provide fuels for fetal growth and energy needs.

- Dr Patrick Catalano

Gestational Diabetes Mellitus (GDM) is defined as *'carbohydrate intolerance with recognition or onset during pregnancy'*, irrespective of the treatment with diet or insulin. The importance of GDM is that two generations are at risk of developing diabetes in the future. Women with a history of GDM are at increased risk of future diabetes, predominately type 2 diabetes, as are their children[1]

GDM occurs when the woman's beta cell function is not able to overcome the antagonism created by the anti-insulin hormones of pregnancy and the increased fuel consumption required to provide for the growing fetomaternal unit.

- Dr Alberto de Leiva

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*Based on the deliberations of the First National Conference of Diabetes In Pregnancy Study Group India at Chennai, February 11 and 12, 2006.

Screening

The controversy concerning optimal strategy still continues for the detection and diagnosis of GDM. American Diabetes Association (ADA) recommends two step procedures for screening and diagnosis of diabetes and that too in selective (high risk) population. Compared with selective screening, universal screening for GDM detects more cases and improves maternal and neonatal prognosis.[3] In the Indian context, screening is essential in all pregnant women as the Indian women have 11 fold increased risk of developing glucose intolerance during pregnancy compared to Caucasian women.[4] The recent data on the prevalence of GDM in our country was 16.55% by WHO criteria of 2 hr PG ≥ 140 mg / dl.[5] As such Universal screening during pregnancy has become important in our country. For this we need a simple procedure which is economical and feasible.

DIPSI Recommended Method

As a pregnant woman walks into the antenatal clinic in the fasting state, she has to be given a 75g oral glucose load and at 2 hrs a venous blood sample is collected for estimating plasma glucose. This one step procedure of challenging women with 75 gm glucose and diagnosing GDM is simple, economical and feasible.[6]

Diagnostic Criteria

American Diabetes Association (Carpenter and Couston) recommends 3 hour 100 gm OGTT and Gestational Diabetes Mellitus is diagnosed if any 2 values meet or exceed FPG ≥ 95 mg / dl, 1 hr PG ≥ 180 mg / dl, 2 hr PG ≥ 155 mg / dl and 3 hr PG ≥ 140 mg / dl. This criteria was originally validated against the future risk of these women developing diabetes and not on the fetal outcome. Carpenter himself now recommends a 2 hour OGTT with 75 gm glucose. The reason for this is that "when a glucose tolerance test is administered to non-pregnant individuals, it is standard to use the 75-g, 2-hour OGTT. Using a different glucose challenge in pregnant versus non-pregnant patients leads to confusion in the laboratory and may result in errors in applying the proper diagnostic criteria. Further, the 75-g, 2-hour OGTT is in use during pregnancy in many countries around the world, typically using the same thresholds as in non-pregnant individuals".[7] To standardize the diagnosis of GDM, the World Health Organisation (WHO) proposed using a 2 hour 75 gm OGTT with a threshold plasma glucose concentration of greater than 140 mg / dl at 2 hour, similar to that of IGT, outside pregnancy.[8] Still all these recommendations (ADA and WHO) have not projected the influence of the glycemic level on fetal outcome.

Clarity in Labelling The Different Magnitude of Abnormal Glucose Intolerance on Pregnancy

Increasing maternal carbohydrate intolerance in pregnant women without GDM is associated with a graded increase in adverse maternal and fetal outcomes[9] implying that fetal morbidity starts at a lower maternal glycemic level (< 140 mg / dl). A number of prospective and retrospective studies have substantiated the observation that the frequency of adverse fetal outcome increases with 2hr PG ≥ 120mg / dl and taking care of these women had resulted in a better fetal outcome.[10-14] Thus, the data is robust and indicates that 2 hr ≥ 120mg / dl needs cognizance.

The term 'Impaired Gestational Glucose Tolerance (IGGT)' is used by few authors to indicate pregnant women whose 2 hr PG is > 120mg / dl. It may be appropriate to use the term 'Decreased Gestational glucose tolerance (DGGT)' instead of impaired gestational glucose tolerance. The use of the term 'Decreased' is appropriate as it implies only 'Low' whereas the term 'Impaired' means both high and low. Further, quiet frequently we come across, labeling any abnormal value in the OGTT not meeting the diagnostic criteria of GDM as IGT.[15] The use of this term 'IGT' during pregnancy may be confusing, as this terminology is also being used in non pregnant adult with 2 hr PG ≥ 140 mg / dl. This level is also applied to diagnose GDM by WHO criteria. Hence it may be prudent to label 2 hr plasma glucose value ≥ 140 mg / dl as GDM and a 2 hr plasma glucose value ≥ 120 mg / dl as 'Decreased Gestational Glucose Tolerance' (DGGT). The term IGT should not be used to denote any abnormal value during pregnancy. The figures suggested below are easy to remember.

With 75 gm OGTT (WHO criteria);

	In Pregnancy	Outside Pregnancy
2 hr ≥ 200 mg / dl	Diabetes	Diabetes
2 hr ≥ 140 mg / dl	GDM	IGT
2 hr ≥ 120 mg / dl	DGGT	—

Gestational Weeks at Which Screening is Recommended

Practically all the pregnant women should undergo screening for glucose intolerance. The usual recommendation for screening is between 24 and 28 weeks of gestation. The recent concept is to screen for glucose intolerance in the first trimester itself as the fetal beta cell recognizes and responds to maternal glycemic level as early as 16th week of gestation.[16] If found negative at this time, the screening test is to be performed again around 24th – 28th week and finally around 32nd – 34th week.

Management Of GDM

A team approach is ideal for managing women with GDM. The team would usually comprise an obstetrician, diabetes physician, a diabetes educator, dietitian, midwife and pediatrician. In practice, however, the team approach is not always possible due to limited resources.

In such circumstances, management by an obstetrician and physician, with the assistance of an appropriately skilled dietitian, diabetes educator, is acceptable.

A) Patient Education

The importance of educating women with GDM (and their partners) about the condition and its management cannot be overemphasized.

The compliance with the treatment plan depends on the patient's understanding of:

- The implications of GDM for her baby and herself
- The dietary and exercise recommendations
- Self monitoring of blood glucose
- Self administration of insulin and adjustment of insulin doses
- Identification and treatment of hypoglycemia (patient and family members)
- Incorporate safe physical activity
- Development of techniques to reduce stress and cope with the denial.

Care should be taken to minimise the anxiety of the women.

B) Medical Nutrition Therapy (MNT)

a) *General Principles* : All women with GDM should receive nutritional counseling. The meal pattern should provide adequate calories and nutrients to meet the needs of pregnancy. The expected weight gain during pregnancy is 300 to 400 gm / week and total weight gain is 10 to 12 kg by term. Hence the meal plan aims to provide sufficient calories to sustain adequate nutrition for the mother and fetus and to avoid excess weight gain and post prandial hyperglycemia. Calorie requirement depends on age, activity, pre pregnancy weight and stage of pregnancy. Approximately 30 to 40 Kcal / kg ideal body weight or an increment of 300 kcal / day above the basal requirement is needed. Pregnancy is not the ideal time for obesity correction. Underweight subjects or those not gaining weight as expected, particularly in the third trimester, require admission to ensure adequate nutrition to prevent low birth weight infants.

b) *Calorie Counting* : As a part of the medical nutrition therapy, pregnant diabetic woman are advised to wisely distribute their calorie consumption especially the breakfast. This implies splitting the usual breakfast into two equal halves and consuming the portions with a two hour gap in between. By this the undue peak in plasma glucose levels after ingestion of the total quantity of breakfast at one time is avoided. For example if 4 idlis / chappathi / slices of bread (applies to all type of breakfast menu) is taken for breakfast at 8 am and two hours plasma glucose at 10 am is 140mg: the same quantity divided into two equal portions i.e., one portion at 8 am and remaining after 10 am, the two hours post prandial plasma glucose at 10.00 am falls by 20 – 30 mg.

This advice has scientific basis as the peaking of plasma glucose is high with breakfast (due to Dawn phenomenon) than with lunch and dinner. Further in a normal person, insulin secretion is also high with breakfast than with lunch or dinner.[17] GDM mothers have deficiency in first phase insulin secretion and to match this insulin deficiency the challenge of quantity of food at one time should also be less.

Insulin Therapy

Insulin is essential if medical nutrition therapy fails to achieve euglycemia. Various criteria have been proposed for the initiation of insulin therapy. Fourth International Workshop on GDM recommended lowering capillary blood glucose concentration to 140 mg / dl at 1 hour and 120 mg / dl at 2 hours,[18] whereas ADA recommended the option of measuring 1 hour post meal values with cut off of 120mg / dl.[19] These recommendations are based on one single determination, which reflects a "snap shot" of glucose evaluation rather than a "video" of continuous glucose profile.[20] The continuous glucose monitoring system has established that in normal pregnancy, peak plasma glucose occurs at 60 minutes and the value was 108.7 ± 16.9 mg / dl.[1] In a woman with GDM, the peak occurs between 70 – 110 minutes (at approximately 90 minutes) and with a good glycemic control the value was 103 ± 26 mg / dl.[20] However, being interstitial fluid glucose it has its own limitation.

If the FPG concentration on the OGTT is $\geq$120mg / dl, then the patient is started on insulin immediately along with meal plan. Other GDM women are seen within 3 days and are also taught self monitoring of blood glucose (SMBG). SMBG is to be performed in fasting and 1 ½ hours after each meal. GDM women usually have high post breakfast plasma glucose level compared to post lunch and post dinner. A few GDM women do have post dinner plasma glucose also high. Insulin is started within 1 to 2 weeks, if the majority (i.e., at least four of seven per week) of fasting values exceed 90 mg / dl. Similarly, if the majority of post prandial values after a particular meal exceed 120 mg / dl, insulin is started.[21] Pen injectors are very useful and the patient's acceptance is excellent.

The initial dose of NPH insulin could be as low as 4 units and the dose of insulin can be adjusted on follow up. A few GDM patients may require combination of short acting insulin and intermediate acting insulin in the morning and evening.

- If a patient has elevated prelunch blood sugar, regular insulin is usually necessary in the morning to handle the post breakfast hyperglycemia, as there is a lag period before the intermediate-acting insulin begins to work. The above regimen of regular and intermediate-acting insulin in the morning controls hyperglycemia in most cases.

- If the post dinner blood sugar is high, a small dose of regular insulin is necessary before dinner in addition to the regular and intermediate acting insulin given in the morning.
- Combination of regular and intermediate acting insulin before dinner may be necessary if fasting blood sugar is high. This combination of short and intermediate acting insulin in the morning and as well as in the evening is known as mixed and split dose of insulin regimen. In this regimen two-third of the total daily dose of insulin is given in the morning and one third in the evening. For each combination one-third dose should be regular insulin and two-third intermediate acting insulin. With this regimen if the patient continues to have fasting hyperglycemia, the intermediate acting insulin has to be given at bedtime instead of before dinner. Insulin dose is individualized.

Target Blood Glucose Levels

Maintenance of Mean Plasma Glucose (MPG) level ≃ 105 mg% is ideal for good fetal outcome.[22] This is possible if FPG and post prandial peaks are around 90 mg / dl and 120 mg / dl respectively (MPG should not be < 86 mg / dl as this may cause small for gestational age infants).[22]

Species of Insulin

It is ideal to use human insulins are least immunogenic. Though insulin does not cross the placenta, the insulin antibodies due to animal source insulin can cross the placenta, and stress the fetal beta cell, increase insulin production and induce macrosomia. Rapid acting insulin analogues, (Novorapid / Humalog) have been found to be safe and effective in achieving the targeted post prandial glucose value during pregnancy.[23] Lyspro the first analogue to get category B approval by US FDA and aspart has also been used in pregnancy.

Oral Antidiabetic Drugs

Recently reports have shown good fetal outcome in GDM women who were on glyburide (micronised form of Glibenclamide). A randomized unblinded clinical trial compared the use of insulin and glyburide in women with GDM who were not able to meet glycemic goals on meal plan. Treatment with either agent resulted in similar perinatal outcomes. All these patients were beyond the first trimester of pregnancy at the initiation of therapy.[24]

More studies are required before routinely recommending glibenclamide during pregnancy especially during the first trimester itself. Metformin has been found to be useful in women with polycystic ovarian disease (PCOD) who failed to conceive. Continuing this drug after conception is still a controversy. But there are a few studies favouring continuation of metformin throughout pregnancy.[25] Currently, oral agents are not routinely recommended during pregnancy though emerging data on glibenclamide and metformin is interesting.

Monitoring Glycemic Control

The success of the treatment for a woman with GDM depends on the glycemic control maintained with meal plan or pharmacological intervention. To know the effectiveness of treatment, monitoring of glycemic control is essential.

- Once diagnosis is made, medical nutritional therapy (MNT) is advised initially for two weeks. If MNT fails to achieve control i.e., FPG ≥ 90mg / dl and / or 1 ½ hr PPG ≥ 120mg / dl, insulin may be initiated.
- Once target blood glucose is achieved, woman with GDM till the 28th week of gestation require lab monitoring of both fasting and 1 ½ hr post breakfast once a month and at other time of the day as the clinician decides.
- After the 28th week of gestation, the laboratory monitoring should be more frequent atleast once in 2 weeks, if need be more frequently.
- After 32 weeks of gestation, lab monitoring should be done once a week till delivery.
- In high risk pregnancies, frequency of monitoring may be intensified with SMBG.
- Continuous glucose monitoring devices are available but these equipments need special training and are expensive. These devices may be useful in high risk pregnancies to know the glycemic fluctuations and to plan proper insulin dosage.

Throughout the stages and phases of a diabetic woman, her health status is directly dependent on her nutritional status and her blood glucose control. As a woman ages, to prevent the increased risk of osteoporosis and cardiovascular disease of the diabetic woman, exercise and hormonal replacement therapy can minimize the ravages of diabetes per se on the aging process. Normoglycemia throughout the lifecycle of a diabetic woman results in a lifecycle of health.

- Dr Lois Jovanovic

HbA_1c Levels

If the glucose intolerance is detected in the early pregnancy, HbA^1c level will be helpful to differentiate between a pre gestational diabetic and GDM. If the HbA_1c level is more than 6%, she is likely to be a pre GDM. HbA_1c is useful in monitoring the glucose control during pregnancy, but not for the day to day management. A_1c level may serve as a prognostic value. Estimation of fructosamine during pregnancy is less frequently used.

Measuring Other Parameters

The blood pressure has to be monitored during every visit. Examination of the fundus and estimation of microalbuminuria, every trimester is recommended.

e) *Ultrasound Fetal Measurement* : The management of gestational diabetes, based on the foetal growth by ultrasonogram demands that the fetus at risk must first manifest overgrowth before treatment decisions are made. Further, the cost of performing a number of ultrasonograms to monitor the foetal growth and recommending therapy has to be kept in mind. Until there is evidence to absolutely prove that ignoring maternal hyperglycemia when the fetal growth patterns appear normal on the ultrasonogram, it is prudent to achieve and maintain normoglycemia in every pregnancy complicated by gestational diabetes.

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- Dr Lois Jovanovic

Obstetric Considerations

Fetal Evaluation

An ultrasound scan has to be performed around 18 – 20 weeks of gestation focusing on structures namely the spine, skull, kidney and heart. Fetal echocardiography has to be done around 20 – 24 weeks which allows to view all the four chambers of the heart. From 26th week onwards, fetal growth and liquor volume has to be monitored every 2-3 weeks. Fetal abdominal circumference provides baseline for further serial measurements which gives growth acceleration or restriction. Fetal movements are monitored from 20 weeks onwards. Screening for chromosomal anomalies is necessary in pre GDM. Screening should be done for Down's syndrome, alpha feto protein for neural defects and human chorionic gonadotrophin to identify any chromosomal abnormalities (16 – 20 weeks of gestation).

The obese fetus of GDM mother is also hyperinsulinemic, thus interaction between leptin and insulin may be a link between maternal diabetes and increased adiposity in the fetus.

- Dr Sylvie Hauguel-de Mouzon

GDM or severe obesity is superimposed to pregnancy, the resulting metabolic syndrome becomes detrimental for the fetus, evolving towards fetal overgrowth with increased adiposity at birth. This may be one major component for in utero programming of obesity later in life.

- Dr Sylvie Hauguel-de Mouzon

Timing of Delivery

Sudden intrauterine fetal demise in the third trimester of diabetic pregnancy is not uncommon. To avoid this risk, preterm delivery is recommended. But with this, respiratory distress syndrome (RDS) is likely to occur. Administering steroids for lung maturity or ß adreno receptor agonist to inhibit premature uterine contractions are likely to induce adverse metabolic effects due to their glycolytic, glycogenolytic and lipolytic effects. In this situation, extra insulin may be required to maintain euglycemia. Foetal demise can also occur due to preeclampsia, which can produce fetal hypoxia via decreased uteroplacental perfusion. Some centres allow women with uncomplicated diabetes to go into spontaneous labor irrespective of the gestational age, *but most still advocate delivery at 38 weeks* as perinatal mortality and morbidity appear to increase after this time. Induction at 38 weeks gestation may be slow or unsuccessful due to unfavourable conditions of the cervix but this has to be balanced against the poorly defined and predictable risk of late intra uterine death, if pregnancy is allowed to continue more than 38 weeks. Fetal health may deteriorate suddenly, hence obstetric management should not be rigid and each case needs individual care and attention. Having a neonatologist support at the time of delivery is advisable.

Intra Partum Management

- If labor is to be induced in GDM, the usual evening insulin dose should be taken the night before, but no subcutaneous insulin is given the following morning when induction begins.
- Once labor begins, insulin is not necessary.
- In a gestational diabetic the requirement of insulin is likely to fall precipitously and no insulin may be required immediately after expulsion of placenta.

Delivery

A paediatrician experienced in resuscitation of 'the newborn should be present whether delivery is vaginal or by caesarean section. As soon as the infant is born, the following actions are mandatory:

- early clamping of the cord, i.e. within 20 seconds of delivery, to avoid erythrocytosis;
- evaluate vital signs; Apgar scores at 1 and 5 minutes;
- clear oropharynx and nose of mucus; later empty the stomach - be aware that stimulation of the pharynx with the catheter may lead to reflex bradycardia and apnoea;
- avoid heat loss, keep neonate warm, transfer to incubator pre-warmed to 34^{o}C;
- perform a preliminary physical examination to detect major congenital malformations;
- monitor heart and respiratory rates, colour, and motor behaviour for at least the first 24 hours after birth;
- start early feeding, preferably breast milk, at 4-6 hours after delivery: aim at full caloric intake (125 kcal / kg / 24 hours) at 5 days, divided into six to eight feeds a day;
- promote early infant-parent relationship (bonding).

The neonate is usually best cared for, in a specialized neonatal unit. Interference with the infant should be minimal. The neonate should be observed closely after delivery for respiratory distress. Capillary blood glucose should be monitored at 1 hour of age and before the first four breast feedings (and for up to 24 hours in high- risk neonates). Amperometric blood glucose meters are acceptable for use in neonates, provided that suitable quality-control procedures and operator training are in place. The cut-off of 44mg% (2.6 mmol / l) is now currently used as the working definition for hypoglycemia. This "Operational threshold" is not a diagnosis of a disease but an indication for action.[26] If the baby is obviously macrosomic, calcium and magnesium levels should be checked on day 2. Breastfeeding, as always, should be encouraged in women with GDM.

Both maternal pregravid obesity and GDM are significant risk factors for obesity in the offspring of the woman with GDM both at birth and at the time of long term follow up.

- Dr Patrick Catalano

Follow Up Of GDM

GDM may be viewed as:

1. An unidentified preexisting disease, or
2. The unmasking of a compensated metabolic abnormality by the added stress of pregnancy, or
3. A direct consequence of the altered maternal metabolism stemming from the changing hormonal milieu.

Gestational diabetic women require follow up. Glucose tolerance test with 75g oral glucose is performed after 6 weeks of delivery and if necessary repeated after 6 months and every year to determine whether the glucose tolerance has returned to normal or progressed. A small proportion of gestational diabetic women may continue to have glucose intolerance.

Prevention of adverse maternal and perinatal outcomes in GDM are based in achieving maternal blood glucose as close to normal as possible. Precise glycemic thresholds remain undetermined.

Prepregnancy BMI, duration and severity of maternal hyperglycemia during pregnancy, are most important predictors of the progression to abnormal glucose tolerance/ diabetes in the follow up.

- Dr Alberto de Leiva

GDM recurs approximately in 50% of subsequent pregnancies. The future risk of developing diabetes for a gestational diabetic is two fold, if she becomes overweight. But maintaining ideal weight approximately halves the risk. The requirement of insulin in addition to diet to maintain euglycemia during the index pregnancy is also predictive of future diabetes.

The maternal health and fetal outcome depends upon the care by the committed team of diabetologists, obstetricians and neonatologists. A short term intensive care gives a long term pay off in the primary prevention of obesity, IGT and diabetes in the offspring, as the preventive medicine starts before birth.

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