GESTATIONAL DIABETES MELLITUS – CURRENT GUIDELINES FOR DIAGNOSIS & MANAGEMENT

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Pregnancy induces progressive changes in maternal carbohydrate metabolism. As pregnancy advances insulin resistance and diabetogenic stress due to placental hormones necessitate compensatory increase in insulin secretion. When this compensation is inadequate gestational diabetes develops. 'Gestational Diabetes Mellitus' [GDM] is defined as carbohydrate intolerance with onset or recognition during pregnancy. Women diagnosed to have GDM are at increased risk of future diabetes predominantly type 2 DM as are their children [1]. Thus GDM offers an important opportunity for the development, testing and implementation of clinical strategies for diabetes prevention [2]. Timely action taken now in screening all pregnant women for glucose intolerance, achieving euglycemia in them and ensuring adequate nutrition may prevent in all probability, the vicious cycle of transmitting glucose intolerance from one generation to another [3].

EPIDEMIOLOGY

The prevalence of GDM in India varied from 3.8 to 21% in different parts of the country, depending on the geographical locations and diagnostic methods used. GDM has been found to be more prevalent in urban areas than in rural areas [4-11]. For a given population and ethnicity, the prevalence of GDM corresponds to the prevalence of Impaired Glucose Tolerance [IGT, in non-pregnant adult] within that given population [12].

Screening & Diagnosis

A number of screening procedures and diagnostic criteria (ADA, WHO, CDA, NDDG and Australasian criteria) are being followed in the same as well as in different countries. American Diabetes Association (ADA) recommends screening for selective (high risk) population. But compared to selective screening, universal screening for GDM detects more cases and improves maternal and neonatal prognosis [13, 14]. Hence universal screening for GDM is essential, as it is generally accepted that women of Asian origin and especially ethnic Indians, are at a higher risk of developing GDM and subsequent type 2 diabetes [15, 16, 17].

ADA procedure

ADA recommends two step procedures. Step 1: A 50 g glucose challenge test (GCT) is used for screening without regard to the time of last meal or time of the day [18]. Step 2: If 1 hour GCT value is more than 140 mg/dl, 100g Oral Glucose Tolerance Test (OGTT) is recommended and plasma glucose is estimated at 0, 1, 2 and 3 hours. Gestational Diabetes Mellitus is diagnosed (Carpenter and Coustan criteria) 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. The drawback of this criteria is that, the glycemic cut off was originally validated against the future risk of these women developing diabetes and not on the fetal outcome [19]. Further, in the community health centers, pregnant women are reluctant to undergo ADA procedures for two reasons.

1. The number of blood samples drawn are many (a) for screening and (b) for subsequent 3- hour OGTT to confirm the diagnosis (4 blood samples).
2. They have to visit the ante-natal clinic on two occasions – (a) for screening and (b) again for diagnostic procedure due to which the phenomenon of "No show" occurs.

Yet another observation was that, 18-23% pregnant women whose GCT was positive in the first visit, failed to return for the definitive OGTT [20, 21, 22]. Therefore a single step procedure is preferred for the diagnosis of GDM [23, 24].

WHO Procedure

When a glucose tolerance test is administered to a non-pregnant individual, it is standard to use the 75-g, 2-hour OGTT. Using a different glucose challenge in pregnant versus non-pregnant persons leads to confusion in the laboratory and may result in errors in applying the proper diagnostic criteria [25]. To standardize the diagnosis of GDM, the World Health Organization (WHO) recommends using a 2 hour 75 gm OGTT with a threshold plasma glucose concentration of greater than 140 mg/dl at 2 hours, similar to that of IGT (> 140 & < 199 mg/dl), outside pregnancy [26]. WHO procedure also has a shortcoming in that, the criteria suggested for diagnosis of GDM was also not based on the maternal and fetal outcome but probably the criteria was recommended for its easy adaptability in clinical practice.

Table 1 : Glycemic Criteria for Diagnosis of different categories of glucose intolerance by 75 g, 2 hr OGTT

Criteria	*FPG mg/dl*	*2-hr PG mg/dl*
Normal Glucose Tolerance [NGT]	< 100	< 140
Impaired Fasting Glucose [IFG]	100 – 125	-
Impaired Glucose Tolerance [IGT]*	-	140 – 199
Diabetes Mellitus [DM]	≥ 126 and / or	≥ 200

***Glycemic cut-off for the diagnosis of IGT outside pregnancy is the same for the diagnosis of GDM during pregnancy.**

Reconciliation factors between ADA and WHO

GDM based on two hour 75gm OGTT defined by either WHO or ADA Criteria predicts adverse pregnancy outcome [27]. There was no significant difference between prevalence of GDM using Carpenter & Coustan (ADA) and WHO criteria [6, 27]. WHO criteria of two hour PG ≥ 140mg/dl identifying a large number of cases may have a greater potential for prevention of diabetes [27, 28]. The glycemic criteria for diagnosis of different categories of glucose intolerance by 75 g, 2 hr OGTT is listed in table 1.

Significance of 2 hr plasma glucose level of 140 mg/dl (7.8 mmol/l)

Increasing maternal carbohydrate intolerance in pregnant women is associated with a graded increase in the adverse maternal and fetal outcomes [29, 30]. Though there is a continuous relationship between maternal glycemia and neonatal outcomes, the primary outcomes of birth weight, neonatal adiposity and Cord C peptide level > 90th percentile tends to occur as the 2 hr PG increases > 140 mg/dl (7.8 mmol/l) [30]. In yet another follow-up study of children born to mothers who had third trimester plasma glucose, 120-139 mg/dl, the cumulative risk of type 2 diabetes was 19% at age 24 years and this risk increased to 30% with respect to those women who had 2 h plasma glucose 140 -199 mg/dl [31]. Thus both short–term and long-term morbidity in the offspring occurs at the inflection point of maternal 2 hr plasma glucose > 140 mg/dl and as such, this level assumes clinical significance. A pregnant woman, whose 2 hour plasma glucose is 120-139 mg/dl, needs follow-up [32].

A single test procedure to diagnose gestational diabetes mellitus in the community

Seldom, a pregnant woman visiting the ante-natal clinic for the first time comes in the fasting state. If she is asked to come on another day in the fasting state she may not return [19, 20, 21]. Hence it is important to have a test that detects the glucose intolerance without the woman necessarily undergoing a test in the fasting state and it is preferable to perform the diagnostic test at the first visit itself.

In the antenatal clinic, a pregnant woman after undergoing preliminary clinical examination, has to be given a 75g oral glucose load*, without regard to the time of the last meal. A venous blood sample is collected at 2 hours for estimating plasma glucose by the GOD-POD method. GDM is diagnosed if 2 hr plasma glucose is ≥ 140 mg/dl.

** If 75g glucose packet is not available, remove 5 level teaspoons (not heaped) of glucose from a 100 g packet which is freely available. In hospitals where glucose is supplied in bulk, a cup or container of 75 g may be used.*

Table 2 : With 75 gm OGTT (WHO criteria)

Plasma Glucose	In Pregnancy	Outside Pregnancy
2 hr ≥ 200 mg/dl	Diabetes	Diabetes
2 hr ≥ 140 mg/dl & ≤ 199 mg/dl	GDM	IGT
2 hr ≥ 120 mg/dl & ≤ 139 mg/dl	GGI	—
2 hr < 120 mg/dl	Normal	Normal

Performing this test procedure in the non-fasting state is rational, as glucose concentrations are affected little by the time since the last meal in a normal glucose tolerant woman, whereas it will, in a woman with gestational diabetes [33]. After a meal, a normal glucose tolerant woman would be able to maintain euglycemia despite glucose challenge due to brisk and adequate insulin response, whereas, a woman with GDM who has impaired insulin secretion [34], her glycemic level increases with a meal and with glucose challenge, the glycemic excursion exaggerates further [35]. Therefore, this procedure assumes clinical relevance as WHO criteria based on glucose concentration 2 h after 75 g glucose load was able to correctly identify subjects with GDM [24]. Yet another reason for recommending the single step procedure is that, the specificity of ADA screening with 50 gm 1-hr GCT without regard to time of the last meal is low [22]. Hence, instead of performing screening test using 50 gm-1 hr test and then 100 gm OGTT, this single step procedure serves both as screening and diagnostic test for GDM, is simple, economical and feasible [23].

ADVANTAGES

- *The pregnant women need not be fasting [31, 36].*
- *Causes least disturbance in a pregnant woman's routine activities.*
- *Serves as both screening and diagnostic procedure.*

Clarity in Labeling the Different Magnitude of Abnormal Glucose Intolerance in Pregnancy

Increasing maternal carbohydrate intolerance in pregnant women without GDM is associated with a graded increase in adverse maternal and fetal outcomes [29, 37] implying that the fetal morbidity starts at a lower maternal glycemic level (<140 mg/dl). The occurrence of macrosomia was continuum as the 2 h plasma glucose increased from 120 mg/dl [32, 38, 39]. Yet another study on long-term follow-up documented that, the cumulative risk of type 2 diabetes at 24 years in the offspring born to mothers who had third trimester plasma glucose, 120-139 mg/dl was 19% [31]. In the same study, the cumulative risk was found to be 30% in offspring born to women who had 2 h plasma glucose > 140 mg/dl [31]. 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 and ≤ 139 mg/dl as 'Gestational Glucose Intolerance' (GGI). The term IGT is used outside pregnancy and as such should not be used to denote any abnormal value during pregnancy. The nomenclature and glycemic levels suggested in table 2 are easy to remember.

Gestational Weeks at Which Screening is Recommended

Insulin is detectable in the fetal pancreas as early as 9 weeks after conception [40]. An increase in pancreatic beta cell mass and insulin secretion in the fetus occurs by the 16th week of gestation, in response to maternal hyperglycemia [41, 42]. The priming of the fetal beta cells may account for the persistence of fetal hyperinsulinemia throughout pregnancy and the risk of accelerated fetal growth [43], even when the mother enjoys good metabolic control in later pregnancy [44]. This necessitates performing the test procedures to diagnose GDM in the first trimester itself. Further, early detection and care results in a better fetal outcome [45].

By following the usual recommendation for screening between 24 and 28 weeks of gestation, the chance of detecting unrecognized type 2 diabetes before pregnancy (pre- GDM) is likely to be missed [46, 47]. If the 2 – h PG is > 200 mg/dl in the early weeks of pregnancy, she may be a pre-GDM and A1c of > 6 is confirmatory [48] {Normal A1c levels during pregnancy is 5.3 - 6}. A pregnant woman found to have normal glucose tolerance [NGT] in the first trimester, should be tested for GDM around 24th – 28th week and again around 32nd – 34th week and also in later weeks if necessary, particularly when rapid maternal weight gain occurs or fetal macrosomia is suspected [45, 49].

MANAGEMENT OF GDM

A team approach is ideal for managing GDM. The team would usually comprise of, an obstetrician, diabetes physician, a pediatrician, a diabetes educator, dietitian and a midwife/nurse.

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 (walking at usual pace/ arm exercise)
- Development of techniques to reduce stress and cope with the denial.

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

Treatment

Target Blood Glucose Levels

In normal pregnancy, the mean plasma glucose (MPG) + 1 SD value for fasting is 89 mg/dl, and 2 – hour is 122 mg/dl. [Diabetes In Pregnancy Awareness and Prevention [DIPAP, n = 12,056 [4,5,50]] The occurrence of birth weight > 90th percentile (macrosomia) was continuum as fasting plasma glucose increased > 90 mg/dl [50] and the 2 hr plasma glucose > 120 mg/dl [32]. Thus, maintenance of Mean Plasma Glucose (MPG) level ~ 105 to 110 mg/dl is desirable for a good fetal outcome [51, 52]. This is possible if FPG and peak post prandial glucose levels are maintained ~ 90 (80-90) mg/dl and ~ 120 (110 - 129) mg/dl respectively.

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 gestational weeks of pregnancy. Approximately 30 to 40 Kcal/kg i.e. an increment of 300 kcal/day above the basal requirement is needed in 2nd and 3rd trimesters. Though pregnancy is not the ideal time for obesity correction, in an obese pregnant woman, a lower weight gain of 5-6 kg maybe optimal. 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 140 mg/dl: 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/dl. More than 90 % of GDM can be managed by MNT (Observation from the Diabetes in Pregnancy Awareness & Prevention [DIPAP] Project, supported by the Government of Tamil Nadu and World Diabetes Foundation [WDF]).

Explanatory note:

This advice, of splitting the breakfast into two portions, has scientific basis as the peaking of plasma glucose is high with

breakfast (due to dawn phenomenon) than with lunch and dinner. In a normal person, insulin secretion is higher with breakfast than with lunch or dinner [53], whereas, 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.

Initiating Insulin Therapy

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 Post meal glucose > 120 mg/dl, insulin may be initiated.

A. Preferable to start with Premix insulin 30/70 of any brand *

- Starting dose: 4 units before breakfast

↓

- Every 4th day increase 2 units till 10 units

↓

- If FPG remains > 90 mg/dl, advised → 6 units before breakfast & 4 units before dinner
- Review with blood sugar test → Adjust dose further
- Total insulin dose per day can be divided as 2/3 in the morning and 1/3 in the evening.
- * Initially if Post breakfast plasma glucose is high → Start Premix 50/50

B. If GDM is diagnosed in the third trimester, MNT is advised for a week. Insulin is initiated if MNT fails.

C. If 2- hour PG > 200 mg/dl at diagnosis, a starting dose of 8 units of premixed insulin could be administered straightaway before breakfast and the dose has to be titrated on follow-up. Along with insulin therapy, MNT is also advised.

Insulin Analogs

If Post prandial glucose is still not under control – consider using rapid-acting insulin analogs.

Rapid acting insulin analogues, (Aspart - Novorapid/ Lispro -Humalog) have been found to be safe and effective in achieving the targeted post prandial glucose value during pregnancy [54]. Lispro analogue is approved by US FDA and Aspart has been approved for use in pregnancy both by US FDA and European Union. BIAsp (Novomix) has been found to be safe and effective in the management of GDM [55].

Pen injectors are very useful and the patient's acceptance is excellent.

Note:

1. Usually women with gestational diabetes do not require > 20 units of insulin per day for glycemic control [40], in comparison to type 1 and type 2 pregnant women whose daily requirement of insulin may be high.
2. Pre-gestational diabetic women during pregnancy may require high dose of insulin. A few may require Multiple-Daily Injections (MDIs), usually given as short acting insulin before breakfast and lunch and intermediate–acting insulin or premix before dinner.
3. Insulin dose is always individualized and has to be adjusted on follow-up.
4. If insulin requirement drops, placental insufficiency or fetal jeopardy has to be suspected (may also be due to increased utilization of maternal glucose by the supercharged beta cell mass of the macrosomic fetus [40] – "*fetal handling of maternal glucose*"**).**

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. Studies suggest 1, 1 ½ and 2 hour post meal for monitoring glycemic control [56-63]. Two-hour post meal monitoring is preferred as the diagnosis of GDM is also based on 2 hour plasma glucose. It is easier to remember this timing, as the time for diagnosis and also for monitoring is the same i.e 2 hours. However, whichever timing is targeted for monitoring glycemic control and adjusting insulin dose, blood tests must be performed at the same time at each visit.

They should be advised to perform self monitoring of blood glucose (SMBG) on a daily basis, failing which, at least weekly monitoring should be encouraged. If self-monitoring is not possible, laboratory venous plasma glucose has to be estimated for adjusting the dose of insulin.

Explanatory note:

GDM women usually have high post breakfast plasma glucose level compared to post lunch and post dinner. The period between breakfast and lunch is often problematical because of the physiological tendency to hyperglycemia at this time, and may necessitate substantial increases in the morning dose of short-acting insulin, together with careful adjustment of meal timing and snacks to avoid hypoglycemia [40]. A few GDM women may have high post lunch and dinner plasma glucose. Insulin dose has to be adjusted by frequent monitoring of postprandial blood glucose.

Oral Antidiabetic Drugs

Insulin secretagogue [Gibenclamide]

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 [64]. Publications on other drugs belonging to this group are dismal.

Metformin

A randomized controlled study found that in women with gestational

Table 3 : Plasma Glucose and Insulin IV Fluid

Plasma Glucose ***At time of onset of labour***	**Insulin / IV Fluids**
< 70 mg/dl	5% GNS - 100 ml/hr
90-120 mg/dl	NS - 100 ml/hr
120-140 mg/dl	NS -100 ml/hr *plus* *4 units of Reg. insulin added with IV fluid*
140-180 mg/dl	NS - 100 ml/hr *plus* 6 *units of Reg. insulin added with IV fluid*
>180 mg/dl	NS - 100 ml/hr *plus* 8 *units of Reg. insulin added with IV fluid*

Drip rate: 16 to 20 drops per minute. Maternal Capillary blood glucose to be checked by glucometer every 1 hour and drip rate adjusted.

diabetes mellitus, metformin (alone or with supplemental insulin) was not associated with increased perinatal complications as compared with insulin [65]. Metformin has been found to be useful in women with polycystic ovarian disease (PCOD) who failed to conceive [66, 67]. Continuing this drug after conception is still a controversy, but there are a few studies favoring continuation of metformin throughout pregnancy in these women [67]. More studies are required before routinely recommending oral anti-diabetic drugs during pregnancy.

Measuring Other Parameters

MATERNAL

If the glucose intolerance is detected in the early weeks of pregnancy, A1c level will be helpful to differentiate between a pre gestational diabetic and GDM. If the A1c level is more than 6%, she is likely to be a pre GDM. A1c is useful in monitoring the glucose control during pregnancy, but not for the day to day management. A1c level may serve as a prognostic value. Although A1C normative data are controversial, the frequency of performing this test may be decided by the Physician taking care of high-risk pregnancy. Follow-up A1C tests need to be performed in the same laboratory for consistency.

The blood pressure has to be monitored during every visit. If blood pressure is found to be more than 130/80, advise alpha-methyldopa 125 mg and dose to be adjusted on follow-up. Examination of the fundus and estimation of microalbuminuria, every trimester is recommended particularly in women with pre-gestational diabetes.

FETAL

Fetal Surveillance

Ultrasound Fetal Measurement: Ultrasound monitoring is recommended every trimester. A fetal echo is a must at 24 week, especially in prediabetics to rule out cardiac defects. In addition, documenting fetal biophysical profile in the late trimester is advisable. Doppler umbilical blood flow measurement or cardiotocograph [CTG] may be performed around 36 weeks of gestation in GDM with other pregnancy complications such as pre-eclampsia, hypertension, ante-partum hemorrhage and intrauterine growth retardation.

Timing of Delivery:

There is a possibility that the diagnosis of GDM may lead to increased obstetric intervention, including induction of labour and caesarean section. Delivery before full term is not indicated unless there is evidence of macrosomia, ployhydramnios, poor metabolic control or other obstetric indications (eg pre-elampsia or intrauterine growth retardation).

Delivery:

During labour, it is essential to maintain good glycemic control [Table 3] while avoiding hypoglycemia. Lower insulin requirements are common during labour (often no insulin is necessary). Maternal blood glucose level should be monitored after delivery, 24 hours post partum and if found to be high, checked again on follow-up. A neonatologist's presence at the time of delivery is ideal, more so if significant neonatal morbidity is suspected.

Neonatal Management:

The neonates of mothers with GDM are also at risk of all complications similar to the infants born to mothers with overt diabetes, particularly those infants born macrosomic [68]. In the Indian population, the normal birth weight of new born babies is between 2.5 – 3.5 kg [69]. Neonates should be monitored closely after delivery for respiratory distress. Capillary blood glucose (cut-off of 44mg/dl ie. 2.6 mmol) should be monitored at 1, 2 and 4 hours after birth and then again before feeding. Early breast feeding is actively encouraged [70]. In nursing pre-GDM mothers, good glycemic control during lactation is advisable by administration of insulin.

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. An OGTT with 75 g oral glucose, using WHO criteria for the non-pregnant population should be performed at 6-8 weeks post-partum. If found normal, GTT is repeated after 6 months and every year to determine whether the glucose tolerance has returned to normal or progressed. A considerable proportion of gestational diabetic women may continue to have glucose intolerance [71].

It is important that women with GDM be counseled with regard to their increased risk of developing permanent diabetes [72, 73]. Indian women with GDM have a high risk of developing diabetes (especially type 2 diabetes mellitus), and metabolic syndrome at a comparatively young age [71, 74]. They should be made aware of the symptoms of hyperglycemia and advice should be given

about the importance of healthy eating and exercise patterns. Contraceptive advice and counseling regarding planning future pregnancies should be given. To avoid occurrence of neural tube defect in an unplanned pregnancy, 0.4 mg dose of folic acid is recommended on a daily basis by Centre for Diabetes Control for all women of child bearing age [75]. The daily requirement of Vitamin B12 during pregnancy is 2.6 mcg which may not be available in a vegan diet. Hence multi-vitamin tablets containing the required amount of B12 in addition to other vitamins maybe recommended. Medical review by a family physician before conception i.e a pre-conception OGTT should be considered.

Women with a history of GDM as well as offspring exposed to maternal diabetes in utero should be a major area of focus for preventive medicine [76]. Preventive measures against Type 2 DM should start during intrauterine period and continue throughout life from early childhood [77]. In conclusion, a short term intensive care gives a long term pay off in the primary prevention of obesity, IGT and diabetes in the offspring, as *preventive medicine starts before birth*. The maternal health and fetal outcome depends upon the care by the committed team of diabetologists, obstetricians and neonatologists.

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