Chapter

35 Gestational Diabetes Mellitus

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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. Pregnancy that occurs in a woman who already has diabetes is termed 'Pre-Gestational Diabetes Mellitus'. Both these situations are associated with increased maternal and fetal morbidity and rarely mortality. The magnitude of these complications is lesser in woman with GDM than in pre-GDM. Universal screening for GDM is strongly recommended for the population ethnically prone to high prevalence of Type 2 DM. The screening around 24 to 28th week is usually done, but it is ideal to test for glucose intolerance in the early pregnancy itself. In much of the world, a 75 gm glucose tolerance test is performed and GDM is diagnosed if 2 hour PG is $\geq$ 140 mg/dl. Pregnant women with gestational diabetes have a significantly increased incidence of cesarean section, pre eclampsia and macrosomia. It has also been observed that increasing carbohydrate intolerance in women without GDM also do suffer from these perinatal complications. Medical nutrition therapy is important in the management of GDM. Women who fail to respond to nutrition therapy are advised insulin and the insulin dose is individualized. Pre GDM has to be on insulin throughout pregnancy including pre conception period. *A short term intensive care not only results in safe motherhood but also 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'.

Diabetes and pregnancy encompasses not only pre gestational diabetes mellitus but also any form of abnormal glucose tolerance during gestation.

a. *Pre-gestational diabetes:* The term pre-gestational diabetes denotes conception in a woman who is already a diabetic.
b. *Gestational diabetes mellitus (GDM):* GDM is defined as any degree of glucose intolerance with onset or first recognition during pregnancy. The definition applies whether insulin or only diet modification is used for treatment and whether or not the condition persists after pregnancy. It does not exclude the possibility that unrecognized glucose intolerance may have antedated or begun concomitantly with pregnancy. The prevalence may range from 1 to 16% of all the pregnancies, depending on the population studied and diagnostic test employed.

Who is at Risk for GDM?

The expert committee on diagnosis and classification of diabetes has recommended that screening may not be necessary in women who fulfill the criteria given in Table 1[1].

Table 1: 'Low-Risk' states where screening is not required

• Age < 25 years
• Weight normal before pregnancy
• Member of an ethnic group with a low prevalence of GDM
• No known diabetes in first-degree relatives
• No history of abnormal glucose tolerance
• No history of poor obstetric outcome

But in the Indian context, recognition of glucose intolerance during pregnancy is perhaps more relevant as Indian women have an eleven fold increased risk of developing GDM compared to white Caucasian women[2]. It is important to detect these GDM cases, because if unrecognized, the pregnancy may end in fetal

wastage or the child may be at higher risk of diabetes in adult life.

Abnormal glucose tolerance of any etiology, recognized or unrecognized, starting before pregnancy or revealed during pregnancy, is associated with a high risk of poor outcome of pregnancy. As glucose is toxic to the developing fetus, ideally all pregnant women should undergo screening for glucose intolerance but screening is mandatory for high-risk patients likely to develop GDM (Table 2).

Table 2: Indications for screening

- Age > 25 years
- Family history of diabetes
- Obesity (Pre-pregnancy BMI>25)
- BOH – previous history of
  - Unexplained perinatal loss
  - IUD
  - Large for gestational age infant
  - Congenitally malformed infant
  - Polyhydroamnios
  - Pre-eclamsia
- Glucose in second fasting urine sample.

What is the Risk?

Gestational diabetes during pregnancy is not only associated with the increasing pregnancy morbidity but also increases the likelihood of subsequent diabetes in the mother. Maternal hyperglycemia has a direct effect on the development of fetal beta cell mass and is associated with increased susceptibility to the development of obesity and diabetes in the offspring. This effect on the offspring is independent of genetic factors[3]. Hence GDM has implications beyond the index pregnancy, identifying two generations—mother and her offspring at the risk of future diabetes. About 25% of GDM mothers develop diabetes by 10 years after the index pregnancy. On prospective follow-up at the Diabetes Pregnancy Service Division of Madras Medical College, 28.4% developed diabetes at the end of 10 years.

Prevalence of GDM: The epidemiology of GDM is subject to various factors such as the population to be screened, the screening methods, the gestational weeks for screening and the glycemic criteria for diagnosis. The prevalence of GDM was 2% in 1982[4] [IGT – 2%[5]] which increased to 7.62% in 1991[6] [IGT – 8.2%[7]], and doubled to 16.55% in 2002[8] [IGT – 14.5%[9]].

ADA RECOMMENDS TWO-STEP APPROACHES[1]

An initial screening by measuring plasma glucose one hour after 50 g oral glucose load (glucose challenge test [GCT]) and perform a diagnostic OGTT on that subset of women exceeding the glucose threshold value on the GCT. When the two-step approach is employed, a glucose threshold value > 140 mg/dl (7.8 mmol/L) identifies approximately 80% of women with GDM, and the yield is further increased to 90% by using a cutoff of > 130 mg/dl (7.2 mmol/L).

Carpenter and Coustan Diagnostic Criteria: The American Diabetes Association has adopted Carpenter and Coustan criteria given in Table 3.

Table 3: Diagnosis of GDM

	100 g OGTT	*75g OGTT*
Fasting	95 mg/dl (5.3 mmol/L)	95 mg/dl
1 – hr	180 mg/dl (10 mmol/L)	180 mg/dl
2 – hr	155 mg/dl (8.6 mmol/L)	155 mg/dl
3 – hr	140 mg/dl (7.8 mmol/L)	—

Two or more of the venous plasma concentrations must be met or exceeded for a positive diagnosis.

WHO CRITERIA

WHO recommends using a two-hour 75g OGTT with a threshold plasma glucose concentration of > 7.8 mmol/L (140 mg/dl) at 2 hours similar to that of IGT outside pregnancy[10].

Note:

American Diabetes Association suggests selective screening for GDM. Selective screening is applicable for women belonging to ethnic group with the low prevalence of GDM, whereas ethnically Indian women are more prone to develop glucose intolerance during pregnancy and have eleven fold increased risk compared to White Caucasians necessitating Universal Screening during pregnancy[2]. GDM diagnosed based on two hour 75 g OGTT defined by either WHO or ADA criteria predicts adverse pregnancy outcome[11]. The criteria recommended by WHO is simple and cost effective and is practiced in many centers[12,13]. Further assuming that effective treatment is available, WHO criteria of 2 hour PPG $\geq$ 140 mg/dl identifying a large number of cases may have a greater potential for prevention[11].

Recommendations

For uniform policy, it is recommended that screening for GDM is two hour plasma glucose with 75g glucose and diagnosed if $\geq$ 140 mg/dl.

*It will be advantageous to estimate fasting plasma glucose also as this will help in planning treatment strategy.

Gestational Weeks for Screening: The current recommen-dation is to perform screening test between 24-28 weeks of gestation, though there are reports that claim about 40 to 66% of women with GDM can be detected early during pregnancy[14,15]. Nahum et al also suggest that the ideal period to screen for GDM is around 16 weeks of gestation and even earlier in high-risk groups with a history of fetal wastage[16]. The screening programme for detecting glucose intolerance during pregnancy may be initiated in the early weeks of pregnancy itself[17]. Further, early screening for glucose intolerance and care could avoid some diabetes related complications in women with gestational diabetes[18,19].

Management: The important predictor of fetal outcome either in pregestational or Gestational diabetes is the glycemic control attained immediately before and during pregnancy. The plasma glucose level of normal pregnant women is less than 90 and 120 mg% respectively during fasting and non-fasting states[20]. Hence the best fetal outcome can be expected by maintaining the mean blood glucose level around 105 mg in a pregnant diabetic woman.

Medical Nutrition Therapy (MNT): The expected weight gain during pregnancy is 300 to 400 gm / week and a total weight gain is 10 to 12 kg by term. Hence the meal plan aims to maintain euglycemia and 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, prepregnancy 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 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.

Gestational Diabetes Mellitus: Gestational Diabetic women who fail to respond to meal plan require insulin. American Diabetes Association recommends insulin if medical nutrition therapy fails to maintain fasting plasma glucose <105 mg / dl and 2 hour post prandial <130mg / dl. Fasting or Post prandial plasma glucose exceeding 90 mg or 120 mg% respectively on more than two occasions is an indication for insulin therapy[21]. Glycemic control of GDM with insulin is not that problematic compared to pregestational diabetic. Rarely GDM requires more than 20 units of insulin per day and a single injection of intermediate acting insulin is sufficient. It is ideal to use Human insulin. If post prandial plasma glucose is high with human insulin, the best option is short acting analogues (Aspart / Lispro).

Pre-Gestational Type-I DM: Maintenance of normoglycemia before conception is essential to prevent fetopathy, since the organogenesis is completed by the 6th week after conception, at a time when most of the women are not even aware of their pregnancy. It has been proved in experimental animals and from observations in human pregnancies that glucose has to be normal before conception to avoid congenital malformation. This is possible with prepregnancy counseling.

Two special diagnostic procedures in the first half of pregnancy are relevant to detect any malformation in the fetus who reports after conception. Ultrasonography can diagnose anencephaly, cardiac and spinal abnormalities. Elevated serum alpha fetoprotein at 14 to 16 weeks of gestation indicates neural tube defect.

In a pregestational Type-1 diabetic woman the requirement of insulin may fall during the early part of first trimester and increase as the pregnancy advances and plateaus during third trimester. They may require morning and evening "split and mixed" dose of Insulin (Ref. Chapter on Insulin). A few pregnant women may require less insulin in the last week of pregnancy attributed to fetal handling of maternal glucose. Sudden decrease in requirement of Insulin in the third trimester of pregnancy indicates fetal jeopardy.

Type 2 DM Women: Pre-gestational type 2 diabetic women desiring to become pregnant should also undergo prepregnancy counseling. Pre-pregnancy control of diabetes with insulin is ideal. Sometimes an hitherto undiagnosed Type 2 diabetic woman may progress through the early weeks of gestation at the risk of malformation in her offspring or a known Type 2 Diabetic woman who is already an oral hypoglycemic agent may present to antenatal clinic after conception and at times in second or third trimester of pregnancy. The best course at this juncture is to withdraw oral hypoglycemic agents and introduce insulin. Though oral antidiabetic drugs are not recommended, the outcome in diabetic women who have conceived and continued to be on oral anti diabetic drugs is not gloomy, since many workers have used these drugs successfully in pregnant diabetics. Recently it has been reported good fetal outcome in GDM who were on glyburide (micronized form of glibenclamide). Oral glucose lowering agents have generally not been recommended during pregnancy. However, one 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[22]. A few more studies are required before routinely recommending glyburide during pregnancy.

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.

Insulin Requirement: The insulin requirement varies from person to person, both in type 1 and type 2 diabetic pregnant women. The aim should be to maintain plasma glucose at acceptable level not to unduly worry about the amount of insulin being administered. A few type 2 diabetic women may require very high dose of insulin even more than 150 units / day. One should not be unduly concerned about the dose of insulin, as the aim during pregnancy is to have optimal glucose control for good fetal outcome[23].

Target Blood Glucose Levels: Maintenance of mean blood glucose level around 105 mg% is ideal for good fetal outcome[24]. A study by Karlson and Kjellman from Sweden showed that perinatal mortality is proportional to maternal blood glucose level during the last weeks of pregnancy[25].

Mean glucose level	Perinatal mortality
> 150 mg%	24%
100 to 150 mg%	15%
< 100 mg%	4%

The continuous glucose monitoring has demonstrated that the time interval from meal to peak post-prandial glucose level was approximately 90 mins and was similar in all the evaluated types of diabetic pregnancies (insulin treated or diet only) and is not affected by the level of glycemic control. Moreover, no difference was obtained in post-prandial glycemic profile between breakfast, lunch or dinner[26].

Monitoring Glycemic Control: The tight glycemic control expected during pregnancy warrants intensive monitoring. Urine glucose monitoring is not accurate and reliable due to altered renal threshold during pregnancy, which varies from hour to hour and day to day. Hence glucose monitoring is the best method using instant blood glucose reflectance meters. Glycosylated Hemoglobin (GHb) will indicate retrospective control and patients' compliance and the past performance. The value of GHb, is in ascertaining whether Glycemic control was satisfactory at the time of conception in a known diabetic becoming pregnant, and further follow up during pregnancy. It is not however, very useful in a gestational diabetic for purposes of monitoring and for day-to-day management. Fructosamine estimation would indicate the glycemic control for the past two to three weeks.

Fetal Evaluation

Mid pregnancy (16-20 weeks) to detect fetal anomalies:

- Maternal serum alpha fetoprotein
- Ultrasonography
- Fetal echocardiography

Late pregnancy (28 weeks to delivery) to assess feta wellbeing:

- Maternal assessment of fetal activity
- Nonstress test
- Contraction stress test
- Fetal biophysical profile
- Ultrasonography
- Lecithin-to-sphingomyelin (L / S) ratio, lung profile.

Intrapartum Diabetic Management: The glucose utilization during labor in well-controlled diabetics is uniformly 2.55 mg / kg / min. The best control achieved during pregnancy should not be lost at labor. Plasma glucose should be monitored hourly and maintained at 100 ± 5mg / dl. A satisfactory protocol for adjusting insulin and intravenous solutions during labor is shown in Table 4.

Table 4: Intravenous fluids and insulin requirements for diabetic women during labor

Blood glucose	*Insulin / IV Fluids*
60-90 mg/dl	5% GNS - 100 ml/hour
90-120 mg/dl	NS - 100 ml/hour
120-140 mg/dl	NS - 100 ml/hour plus 4 units of Reg. insulin added with IV fluid
140-180 mg/dl	NS - 100 ml/hour plus 5 units of Reg. insulin added with IV fluid
>180 mg/dl	NS - 100 ml/hour plus 6 units of Reg. insulin added with IV fluid

In a Gestational diabetic the requirement of insulin will fall precipitously and no insulin may be required immediately after expulsion of placenta. In a known diabetic the dose of insulin has to be adjusted by monitoring blood glucose.

Gestational diabetic women require follow up and Glucose tolerance test is repeated after 6 weeks and if necessary after 6 months to determine whether the glucose tolerance has returned to normal. A proportion

of gestational diabetics may develop diabetes in later years.

GDM Likely to Develop Diabetes: 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 scope of diabetes and pregnancy encompasses not only a known diabetic marching through pregnancy (pre gestational diabetes mellitus) but also any form of abnormal glucose tolerance developing during gestation. A known diabetic marching through pregnancy represents only the tip of the diabetic pregnancy iceberg. The abnormal glucose tolerance of any etiology, during pregnancy, is associated with a high risk of a poor outcome like miscarriages, stillbirth, and neonates with heavy birth weight, hypotrophic infants, and small for dates, children with lethal or handicapping congenital malformations which will be morally and socially demanding. The pregnant mother may also develop hydramnios, toxemia, recurrent urinary tract infections etc. These pregnancies must be classified as high risk pregnancies and are to be taken special care of by a team consisting of diabetologist, obstetrician and a neonatologist.

REFERENCES

1. ADA. Clinical practice recommendations 2002. Diabetes care. 2002;25(Suppl 1).
2. Dornhost A, Paterson CM, Nicholls JS, Wadsworth J, Chiu DC, Elkeles RS. High prevalence of GDM in women from ethnic minority groups. Diabetic Med 1992;9(9):820-2.
3. Dornhost A, Beard RW. Gestational diabetes a challenge for the future. Diabet Med 1993; 10(10): 897-905, Diabet Med 1994;11 (10):992-3.
4. Agarwal S, Gupta AN. Gestational Diabetes. J Assoc Physicians India 1982;30:203.
5. Ramachandran A, Jali MV, Mohan V, et al. High prevalence of diabetes in an urban population in south India. BMJ 1988; 297(6648):587-90.
6. Narendra J, Munichoodappa C. Prevalence of glucose intolerance during pregnancy. Int J Diab Dev Countries 1991; 11:2-4.
7. Ramachandran A, Snehalatha C, Dharmaraj D, et al. Prevalence of glucose intolerance in Asian Indians. Diabetes Care 1992; 15: 1348-55.
8. Seshiah V, Balaji V, Balaji MS, et al. Gestational diabetes mellitus in India. J Assoc Physicians India 2004; 52:707-11.
9. Ramachandran A, Snehalatha C, Kapur A, et al. For the Diabetes Epidemiology Study Group in India (DESI). High prevalence of diabetes and impaired glucose tolerance in India: National Urban Diabetes Survey. Diabetologia 2001;44:1094-1101.
10. WHO study group prevention of diabetes mellitus- Geneva. World health org. 1994. (Tech report series 844).
11. Schmidt MI, Duncan BB, Reichelt AJ, Branchtein L, Matos MC, Costa e Forti A, et al. For the Brazilian Gestational Diabetes Study Group: Gestational diabetes mellitus diagnosed with a 2-h 75-g oral glucose tolerance test and adverse pregnancy outcomes. Diabetes Care 2001; 24(7):115-55.
12. Pettitt DJ, Bennett PH, Hanson RL, Venkat Narayanan KM, Knowler WC. Comparison of World Health Organization and National Diabetes Data Group procedures to detect abnormalities of glucose tolerance during pregnancy. Diabetes Care 1994;17:1264-8.
13. Moses RG. Is it time to modify the GTT for the diagnosis of gestational diabetes? (Letter) Diabetes Care 1995;18:886.
14. Meyer WJ, Carbone J, Gauthier DW, et al. Early gestational glucose screening and gestational diabetes. J Reprod Med 1996; 41:675-9.
15. Super DM, Edelberg SC, Philipson EH, et al. Diagnosis of gestational diabetes in early pregnancy. Diabetes Care 1991; 14:288-94.
16. Nahum GG, Wilson SB, Stanislaw H. Early pregnancy glucose screening for gestational diabetes mellitus. J Reprod Med 2002; 47(8): 656-62.
17. Seshiah V, Balaji V, Madhuri S Balaji, et al. Early screening for Gestational Diabetes. Diabetes 2006;55 (suppl 1):A 606.
18. Bartha JL, Martinez-Del-Fresno P, Comino-Delgado R. Early diagnosis of gestational diabetes mellitus and prevention of diabetes related complications. Eur J Obstet Gynecol Reprod Biol 2003;109(1):4-44.
19. Seshiah V, Cynthia Alexander, Balaji V, et al. Glycemic control from early weeks of gestation and pregnancy outcome. Diabetes 2006;55 (suppl 1):A 604.
20. Jovanovic–Peterson L. The Diagnosis and management of gestational diabetes mellitus. Clin Diabetes 1995;13:32.
21. Jovanovic L, Bevier WC, Peterson CM. The Santa Barbara County Health Care Services Program: birthweight change concomitant with screening for and treatment of glucose-intolerance of pregnancy: A potential cost-effective intervention. Am J Perinatol 1997;14:221-8.
22. Langer L, Conway DL, Berkus MD, Xenakis EM–J, Gonzales O. A comparison of glyburide and insulin in women with gestational diabetes mellitus. N Engl J Med 2000;343:1134-8.
23. Oded Langer. Maternal Glycemic Criteria for Insulin Therapy in Gestational Diabetes Mellitus. Diabetes Care 1998;21(Suppl 2):B91-8.
24. Langer O, Levy J, Brustman L, Anyaegubunam A, Merkatz R, Divon MY. Glycemic control in gestational diabetes mellitus: how tight is tight enough: small for gestational age versus large for gestational age? Am J Obstet Gynecol 1989;161:646-53.
25. Karlsson K, Kjellmer I. The outcome of diabetic pregnancies in relationship to the mother's blood sugar level. Am J obstet Gynaecol 1972; 112:213-20.
26. Avi Ben-Haroush, Yariv Yogev, Rony Chen, et al. The post prandial glucose profile in the diabetic pregnancy. Am J Obstet Gynecol 2004;191(2):576-81.