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Chapter 1

GDM: Management Recommendations During Pregnancy

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Additional information is available at the end of the chapter

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1. Introduction

Gestational diabetes mellitus (GDM) is currently defined as any degree of glucose intolerance with onset or first recognition during current pregnancy [1-4]. Pregnancy induces progressive changes in maternal carbohydrate metabolic process. As pregnancy advances insulin resistance and diabetogenic stress due to placental contra-insulin hormones necessitate compensatory increase in insulin secretion. When this compensatory mechanism fails due to pancreatic β cells inadequacy gestational diabetes develops. GDM affects 1-2% of all pregnancies. In majority of patients it is mild and can be adequately controlled with diet alone but a minority will require antidiabetogenic agents like glyburide or insulin.

Abnormalities of carbohydrate metabolism occur during pregnancy lead to glucose intolerance. Due to diabetogenic effect of pregnancy about 3-5% of all pregnant women show glucose intolerance and approximately 90% of these women have GDM. Majority of these women will have normal carbohydrate tolerance after delivery. However, 50% of women with GDM will develop type 2 DM later in their life. Asian women are ethnically more prone to develop glucose intolerance compared to other ethnic groups. Due to many adverse effects of GDM on mother and foetus early diagnosis and appropriate management is essential for improved outcome of pregnancy.

2. How does pregnancy cause carbohydrate intolerance?

As pregnancy advances it causes

a. Increased insulin resistance due to

1. Antagonistic effect of increased production of human placental lactogen
2. Anti-insulin effect of increased production of placental cortisol, oestriol and progesterone.
3. Increased insulin catabolism by placental and renal insulinase [5]

b. Increased blood glucose level because

1. Mother utilized fat for her caloric requirements and saves glucose for her foetus.

As a result of these physiological changes the normal blood sugar pattern in pregnant woman is Fasting - 65 ± 9mg/dl, non fasting - 80 ± 10 mg/dl, postprandial - 140 ± 10 mg/dl [6].

3. Adverse effects of GDM

Carbohydrate intolerance during pregnancy or GDM causes significant increases in foetal and maternal morbidity. The maternal consequences are

- Preeclampsia: 10-25% of all pregnant diabetes.
- Infection: High incidence of chorioamnionitis and postnatal endometritis.
- Polyhydramnios
- Postpartum bleeding- High incidence due to exaggerated uterine distension.
- Caeserean section: High incidence due to fetal cause.
- Delayed wound healing or wound dehiscence if GDM is not controlled
- Long term effect is type 2 DM.

Fetuses are much more affected than mothers. The fetal consequences are

- Congenital anomaly: It is associated with poor glycemic control and end organ damage.
- Macrosomia: It is defined as a birth weight greater than or equal to 4000 g. Incidence is 17-29% of pregnancies with GDM as compared with 10% in the nondiabetic population [7].
- Hypoglycemia The incidence of neonatal hypoglycemia is greater in GDM than normal pregnancies [8].
- Hypocalcaemia
- Hyaline membrane disease
- Apnea and bradycardia
- Traumatic delivery: The incidence of shoulder dystocia with brachial plexus damage and clavicular fractures are increased in neonates of women with GDM [9]
- Stillbirth

The neonatal morbidity is assessed by a composite outcome that includes stillbirth, neonatal macrosomia or LGA, neonatal hypoglycemia, erythrocytosis and hyperbilirubenemia. Langer et al found composite morbidity in 59% of untreated GDM, 18% of treated GDM and in 11% of non-diabetic subjects [9]. The most common complication was macrosomia which affected 46% and 19% of the newborns from untreated and treated mothers with GDM respectively.

4. How to diagnose GDM?

To diagnose GDM first of all screening is done to detect the potential cases for GDM. A number of screening procedures and diagnostic criteria are followed in different countries like American Diabetes Association (ADA), World Health Organization (WHO), Canadian Diabetes Association (CDA), National Diabetes Data Group (NDDG) and Australian criteria. Two types of screening methods are adopted by different populations. In selective screening, only high risk populations are screened and in universal screening, all pregnant women are included. American Diabetes Association (ADA) recommends screening of selective (High risk) population. But compared to selective screening, universal screening for GDM detects more cases and improves maternal and neonatal prognosis [10]. So universal screening appears to be the most reliable and desired method for detection of GDM [11].

ADA screening: ADA recommends two step screening.

Step1:- A 50 gm glucose challenge test (GCT) is used for screening without regard to the time of last meal or time of the day [12)

Step 2:-If 1hour GCT value is more than 140 mg/dl, 100 g oral glucose tolerance test (OGTT) is recommended and plasma glucose is estimated at 0,1,2 and 3 hours. GDM is diagnosed if any 2 values meet or exceed fasting plasma glucose (FPG) >95 mg/dl, 1 hour postparandial glucose (PG)> 180 mg/dl, 2 hour PG> 155 mg/dl and 3 hour PG >140 mg/dl. But drawback of this method is that, the glycaemic control cut-off was originally validated against the future risk of mother only and on the foetal outcome [13]. Other problems are the number of blood samples requirement is more, 1 for screening and 4 for 3 hour OGTT to confirm the diagnosis. Moreover, patients have to visit the antenatal clinic at least on two occasions for diagnosis leading to their inconvenience.

WHO procedure: To standardize the diagnosis of GDM the World Health Organization (WHO) recommends using a 2 hour OGTT with a threshold plasma glucose concentration of greater than 140 mg/dl at 2 hours, similar to that of impaired glucose tolerance (IGT) in non pregnant state [14]. WHO procedure also was not based on maternal and foetal outcome but probably the criteria was recommended for its easy adaptability in clinical practice. WHO criteria of 2 hour plasma glucose ≥140 mg/dl identifying a large number of cases may have greater potential for prevention of GDM [15].

A single test procedure for diagnosis of GDM: All the diagnostic criteria require the women to be fasting. For successful implementation of universal screening the procedure should not impose any restriction. So a single test 2-hours after 75 g glucose in a non-fasting state

irrespective of last meal can make the diagnostic procedure simple, feasible and economical. It serves as both screening and diagnostic procedure, causes least disturbance to a pregnant woman's routine activities and avoids the inconvenience of fasting in a pregnant woman. It was found that there was no significant difference in PG level between 75g glucose testing in fasting and non-fasting state, irrespective of last meal timing [16]. Performing this test procedure in the non-fasting state is rational, as glucose concentration are affected little by the time since last meal in a normal glucose tolerant woman, whereas meal timing affects in a woman with GDM [17] The non-fasting 2-h post 75 g glucose correctly identified subjects with GDM [18] and strongly predict adverse outcome for the mother and her offspring [19]. Thus, the single test procedure performed irrespective of the last meal timing is seems to be a more rational and patient friendly approach.

Diagnosis	Fasting plasma glucose (FPG) (Mg/dl)	2-hour plasma glucose (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	≥200

Table 1. Classification of glucose intolerance by 75gm 2 hour oral glucose tolerance test(OGTT)

5. When to screen in pregnancy?

Increasing maternal carbohydrate intolerance in pregnant woman without GDM is associated with adverse maternal and foetal outcome [20]. By following the usual recommendation for screening between 24-28 weeks of gestation many early onset of GDM and pre pregnant unidentified diabetes mellitus (DM) can be missed, which may adversely affect foetal outcome. Seshiah et al detected 16.3% glucose intolerance within 16 weeks of pregnancy [21]. Other two studies reported about 40% to 66% of women with GDM can be detected early during pregnancy [22,23]. Nahum et al suggested 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 foetal wastage [23]. GDM diagnosis may not be missed by screening around 24-28 weeks of gestation but a substantial number of pregnant women who develop GDM in the earlier weeks of gestation are likely to have delayed diagnosis and may not receive appropriate medical care. So it is safe to screen for GDM during early weeks of pregnancy as by early detection of glucose intolerance during pregnancy and adequate care to the antenatal women a good foetal outcome can be achieved similar to that of normal glucose tolerance (NGT) pregnant women [24, 25]. If a woman is found to have normal glucose tolerance test in the first trimester, she should be tested for GDM around 24^{th} -28^{th} weeks and around 32^{nd}-34^{th} weeks and also in later weeks if necessary, particularly when rapid weight gain occurs or foetal macrosomia is suspected [26].

It has been suggested that women at high risk should be screened as soon as pregnancy is confirmed [27].

6. High risk GDM

Gestational diabetes is a complication during pregnancy which affects both mother and foetus. From foetal point of view adverse affects are sometimes severe and fatal. Some GDM patients are at higher risk for complications than others. High risk GDM patients are those who have the

- History of stillbirth, neonatal death and foetal macrosomia in previous pregnany
- Maternal obesity and hypertension
- Development of oligohydramnios, polyhydramnios, preeclampsia
- Inadequate metabolic control by diet alone.

Women at high risk should be identified soon after the diagnosis is made, because they need meticulous management to prevent such complications, need antepartum foetal surveillance testing and may require delivery before their expected date of delivery.

7. Management strategies

To prevent maternal and fetal complications treatment at appropriate time is necessary. Early detection of glucose intolerance during pregnancy and instillation of treatment at earliest state can prevent the complications and a good fetal outcome can be achieved.

So, aim of management is to

- Maintain euglycemia
- Prevent obstetrical complications
- Fix optimal time and appropriate mode of delivery

Management includes

1. Counseling of the patient

It is important to counsel the patient with GDM about the condition and its management, so that they can acquire a clear understanding of the characteristics and demands be emphasized on

1. the importance of exercise and diet control

2. importance of blood glucose control

3. self monitoring of blood glucose

4. identification and treatment of hypoglycemia.

2. Treatment of blood glucose control

The fundamental objective of the care of every insulin dependent pregnant diabetic is control of blood glucose to a desirable level for good fetal outcome. The aim is to maintain the fasting glucose level between 80-90mg/dl and 2 hours postprandial glucose level between 110-129mg/dl.

7.1. Medical Nutrition Therapy (MNT)

Dieting is an important step for blood glucose control. But pregnancy needs extra calories for growth and development of fetus. So GDM patients need strict maintenance of diet to maintain adequate calories without affecting blood glucose level to have a healthy baby. The concept of dietary management of the GDM or any other diabetic pregnant woman is that a healthy diet for them is not different from a healthy diet for any other non-diabetic pregnant woman. Patients should know that carbohydrate containing food increase blood glucose levels above normal limits and that persistently abnormal elevation of the blood glucose levels are harmful both for mother and foetus. So to prevent abnormal glucose levels a food plan should be made to maintain adequate calories without affecting blood glucose levels. Patient needs to understand the quantity or servings of carbohydrate present in her meals and snacks and the effect of different types of carbohydrate on her blood glucose levels.

The meal pattern should provide adequate calories and nutrients to meet the needs of pregnancy. The expected weight gain during pregnancy is 300-400g/week and total weight gain is 10-12 kg by term. So the meal plan aims to provide sufficient calories to sustain adequate nutrition for the mother and foetus and to avoid excess weight gain and postprandial hyperglycemia. Calculation of daily caloric intake is based on body weight, age, physical activities and gestational age. Approximately 30-40 kcal/kg and an increment of 300 kcal/day above the basal requirement are needed in 2^{nd} and 3^{rd} trimester. For majority of women with GDM the optional total daily caloric intake will be between 2000 and 2500 cal/day. The total caloric intake is split into three meals and one to three snacks depending on the patient's habit. In a non-diabetic woman the peaking of the plasma glucose is high after breakfast due to "Dawn phenomenon''and the insulin secretion also matches the glycemic excursion that occurs with the meal [28]. But GDM mothers have deficiency in first phase insulin secretion leads to increased postprandial glucose level after heavy breakfast. To avoid the postprandial plasma glucose peaking with breakfast, it can be split into two halves and consuming these portions with a two-hour gap. By this, the undue peak in plasma glucose levels after ingestion of the total quantity of breakfast at one time is avoided.

The total daily caloric allowance should be distributed among the different foods groups in such a way that approximately 40-50% of the calories come from complex carbohydrate. The carbohydrate component of the diet should be distributed as 10-15% at breakfast, 20-30% at lunch and 30-40% at dinner. Approximately 30-40% from fat and the rest from protein. Postprandial elevations of blood sugar are due almost exclusively to the carbohydrate content of the diet. So carbohydrate should be taken as small frequent meal. Growthwer et al showed

the benefit of MNT is series of 1000 pregnant women in comparison to routine care. Serious complications were 1% in MNT and 4% in routine care. Macrosomia rate was 10% in MNT and 21% in routine care. There was no perinatal death in MNT group whereas 5 perinatal deaths were in routine care [29]. Benefits of MNT are

- Decreases hospital admission.
- Decrease in insulin use.
- Improved likelihood of normal foetal and placental growth.
- Reduced risk of perinatal complications specially when diagnosed and treated early

7.2. Oral antidiabetic agents

Oral hypoglycemic agents can be used to control blood glucose where nutritional therapy is failed. Two important agents are used.

Glibenclamide: Glibenclamide (Glyburide) is safe therapy for many GDM women. This drug decreases the insulin resistance and improves insulin secretion. Placental transfer of glybenclamide is negligible. Langer et al concluded that glyburide is as effective as insulin in maintaining the desired glycemic levels and resulted in a comparable outcome [30]. Only 4% of women in the glyburide group were not adequately controlled and required insulin. The usual starting dose of glyburide is 2.5 mg once or twice daily. A randomized clinical trial comparing the effect of insulin and glyburide showed equally good glycemic control and similar perinatal outcome [31]. The total daily dose may be increased up-to 20 mg if necessary. The peak plasma level occurs 2-4 hours after administration and duration of action is 10-12 hours. Women with fasting hyperglycemia but normal postprandial blood glucose may do well with a single dose of glyburide at bed time. Glyburide is a sulfonylurea and its primary mechanism of action is stimulation of the release of insulin from the storage granules of pancreatic beta cells. Secondarily it decreases insulin resistance. It is nonteratogenic and is classified as a category B drug. The main side effect of glyburide is hypoglycemia.

Metformin: Though use of metformin in pregnancy is controversial, studies shows that it can prevent the development of GDM in high risk for developing that. There were no adverse effects to fetus and mother [32, 33]. Metformin trial in gestational diabetes found that in women with GDM, metformin was not associated with increased peinatal complications as compared with insulin [34]. Usual dose is 500 mg to 1500 mg daily in divided doses. Metformin appears to suppress hepatic glucose uptake and decreases intestinal absorption of glucose. It is also a category B drug and it does not cause hypoglycemia. More studies needed before recommendation for routine use in pregnancy.

7.3. Insulin therapy

Once diagnosis is made, nutrition therapy is advised. If it fails oral antidiabetic agents can be tried. If oral agents failed to acheive FPG of ≤ 5.0 mmol/L and 2-h postprandial glucose level of ≤ 6.7 mmol/L insulin is to be started. The aim is to maintain the postprandial peak plasma

glucose level of ≤ 6.7 mmol/L. Human insulin is the insulin of choice for the first time. Most patients require a mixture of intermediate (NPH) and regular (short acting) insulin twice daily. It is preferable to start with premix insulin (mixture of NPH and regular insulin) of any brand. Usually women with GDM do not require >20 unit insulin per day for glycemic control [35]. Recommended dosing schedule is two thirds of the total insulin dose is to be given in the morning and remainder before dinner. The morning dose should be two thirds NPH and one third short acting insulin and the pre-dinner dose should be equal parts NPH and short acting insulin. However, dose schedule requires modification according to patent's BMI, glucose level and life style.

Insulin analogue: If postprandial glucose is still not under control, rapid acting insulin analogue is to be considered. Rapid acting insulin analogues (Aspart-Novorapid, Lispro-Humalog) have been found to be safe and effective during pregnancy. Pregestational diabetic women during pregnancy may require high dose of insulin. A few may require multiple-daily injections usually given as short acting insulin before breakfast and lunch and intermediate acting insulin or premix before dinner. Insulin dose is always individualized and has to be adjusted according to need of the patient.

8. Monitoring of glycemic control:

8.1. Measuring blood glucose level

Meticulous monitoring is essential to achieve desired level of plasma glucose and to prevent post-insulin hypoglycemia. The success of treatment for a woman of GDM depends on glycemic control. Two hours postprandial blood glucose monitoring is preferable as the diagnosis of GDM is also based on two hour plasma glucose. GDM women have high post-breakfast plasma glucose level compared to post lunch and post dinner. So increased morning dose of short acting insulin is needed together with careful adjustment of meal timing and snacks to avoid hypoglycemia.

Once targeted blood glucose level is achieved woman with GDM require monitoring of both fasting and 2-h post breakfast glucose once in a month till 28th weeks of gestation. After 28th weeks blood glucose monitoring should be done fortnightly or more frequently if needed. After 32 weeks blood glucose monitoring should be done once a week till delivery. In high risk pregnancies continuous glucose monitoring may be needed to know the glycemic fluctuations and to plan proper insulin dosage.

8.2. Measuring HbA1c

A1c level is useful in monitoring the glucose control during pregnancy, but not for the day to day management. It serves as a prognostic value. In euglycemic state A1c value should be ≤6%. In early weeks of pregnancy A1c level is helpful to differentiate GDM from pre-pregnant diabetes. If A1c level is more than 6% it indicates that woman is pre GDM [36]. Though treatment approach is not changed based on A1c level.

8.3. Foetal surveillance

The management of GDM, based on the foetal growth and developmental defect if there is any. USG is the key diagnostic tool to detect developmental defect as well as to monitor the foetal growth. Low risk GDM patients who have glycemic control with diet alone and who do not develop any complications like polyhydaramnios, pre-eclampsia or macrosomia need ultrasonogram around 24 weeks of gestation and thereafter as needed. High risk GDM patients who are on insulin or oral antidiabetic agent should have antepartum foetal surveillance by ultrasonogram in every trimester. A foetal echo is a must at 24 weeks to rule out congenital defect. In last trimester biophysical profile is recommended twice in a week or weekly if foetus is at risk.

8.4. Timing of delivery

Low risk or uncomplicated GDM patients may be allowed to develop spontaneous labour and to deliver at term. There is no need to deliver before term unless there is evidence of macrosomia, polyhydarmnios, poor glycemic control or other obstetric complications like, pre-eclampsia or intrauterine growth retardation. Once the uncomplicated GDM patient reaches 40 weeks labour should be induced if cervix is ripe. If cervix is not ripe and estimated foetal weight (EFW) is >4000 gm elective caesarean section is to be done. High risk GDM patients should have their labour induced when they reach 38 weeks. Again C/S is to be done if EFW is >4000 gm. Preterm pregnancy termination may be needed in GDM with complications like pre-eclampsia, polyhydramnios, foetal compromise (less foetal movement) and uncontrolled diabetes. Glucocorticoid for 48 hours should be administered to accelerate lung maturity in preterm termination. Insulin requirement may be increased due to hyperglycemin effect of glucocorticoids. Spontaneous preterm labour is common in patient with GDM. Tocolysis in the form of magnesium sulphate or nifedipine can be used in preterm labour to delay delivery so that glucocorticoid therapy to accelerate lung maturity can be administered over 48 hours.

8.5. Management during labour

Most insulin treated GDM do not need insulin during labour and after delivery. During labour it is essential to monitor blood glucose every 2-4 hours. Upward deviations from normal are corrected with small doses of regular insulin or low dose IV insulin to maintain blood glucose between 100 and 120 mg/dl. If blood glucose is >120-140mg/dl, 4 unit insulin, if >140-180mg/dl 6 unit insulin and if >180 mg/dl 8 unit insulin is to be given in a drip of normal saline at a rate of 16-20 drops/m. Maternal capillary blood glucose is to be checked by glucometer every 1 hour and drip rate is to be adjusted. Dextrose infusion should be avoided. If it is given neutralizing dose of insulin is to be given. 1 unit insulin is needed to neutralize 2.5g glucose. So to neutralize the glucose of 1000 ml 5% dextrose saline 20 unit insulin is to be added with the drip. Drip rate is to be judged according to patient's requirement. Oral feeding is to be started as early as possible to avoid infusion of fluid. Monitoring should be done after delivery and 24 hours postpartum. Usually blood glucose level falls to baseline after delivery.

8.6. Neonatal management

A neonatologist should be present during delivery as GDM is a high risk pregnancy and there is chance of neonatal morbidity. Neonates are at risk of all complications similar to the infants

born to mothers with overt diabetes [37]. Neonates should be monitored closely after delivery for respiratory distress. Capillary blood glucose should be monitored at 1, 2 and 4 hours after birth and before starting of feeding. Cut-0ff value is 2.6 mmol. Early breast feeding is strongly encouraged. If mother's blood glucose is not normalized insulin is advisable in lactating woman for good glycemic control.

9. Prevention of type 2 Diabetes Mellitus (DM)

There is increased risk of development of type 2 DM in patients of GDM [38] and incidence of type 2 DM is about 44% in patients who required insulin or OHA or onset of GDM before 24 weeks [39]. GDM may also recur in a future pregnancy and approximately 55% of patients who were obese or with macrosomic infants will have GDM in subsequent pregnancy [40]. So it is important to perform a 75 g GTT at 6-8 weeks postpartum. If found normal, GTT is repeated after 6 months and every year to assess glucose tolerance. Patients should be informed that about 40-60% of them will have overt diabetics when they are in their 5^{th} decades. Weight loss, dietary control and exercise will obviously help to prevent overt diabetes later in life [41]. GDM has a far reaching consequence in predisposing their offsprings to glucose intolerance. Debelea et al found that more than 50% children who were born to women with GDM developed type 2 DM by the age 35 [42]. The important aspect of GDM is that the intrauterine milieu whether one of nutritional deprivation or nutritional plenty, results in foetal pancreatic development and peripheral response to insulin that may lead to adult onset GDM and type 2 DM[43]. So the timely action in all pregnant women with glucose intolerance to achieve euglycemia may prevent transmitting glucose intolerance from one generation to another [44].

GDM women are at increased risk of future type 2 diabetes mellitus and their children are also at risk of developing type 2 DM later in their life. Universal screening for GDM at early weeks of gestation can detect more cases at an early stage leading to early interventions and hence improves maternal and foetal outcome as early detection leads to early treatment and prevent complications and adverse effect to mother and foetus. A 2-hour 75g post glucose ≥7.8mml/L serves both as screening and diagnostic criteria which is a simple and economical one step procedure. Early detection and treatment of GDM can only prevent the all probable complications and the vicious cycle of transmitting glucose intolerance from generation to generation.

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