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Review Article

GESTATIONAL DIABETES MELLITUS: AN OVERVIEW

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ABSTRACT: The prevalence of diabetes is rapidly rising all over the globe at an alarming rate. Gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance occurring for the first time during pregnancy. The prevalence of GDM varies in direct proportion to the prevalence of Type 2 diabetes for a given ethnic group or population. It is crucial to detect women with GDM as the condition is associated with diverse range of adverse maternal and neonatal outcomes. In addition, having a history of GDM puts the mother at risk for the development of Type 2 diabetes mellitus or recurrent GDM. Various screening guidelines have been introduced depending upon the suitability of test to the population characteristics, cost and screening accuracy. Still there are lots of controversies to which test to be used, when should the screening be done and who should be screened.

However, recognizing GDM is becomimg a major health challenge for clinicians, and treating it results in lowering of both maternal and fetal complications. Also, clinicians must followup women with GDM postpartum so that the prevalence of Type 2 diabetes may start declining.

KEYWORDS: Gestational diabetes mellitus, Oral glucose tolerance test, Oral glucose challenge test

Gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance of varying degrees of severity with onset or first recognition during pregnancy (Balaji V, et.al, 2007).

PREVALENCE

The prevalence of GDM is increasing worldwide especially in developing countries.

In India the prevalence of GDM is high and varies according to geographical areas and diagnostic methods employed (Zargar AH, et.al., 2004 , Divakar H, et.al., 2008). According to a random national survey conducted in 2004 the prevalence was 16.55% (Seshiah V, et.al., 2004). In 2008 , a hospital based survey showed a combined prevalence of GDM and IGT to be 21.6% (Swami SR, et.al., 2008).

RISK STRATIFICATION (Aruna Nigam, et.al.,2010)

Presently according to fifth international workshop conference on GDM, 2005 GDM risk stratification is done at first antenatal visit. The pregnant females are divided into low , middle and high risk and managed accordingly.

Low risk – No blood glucose testing is done if –

- Age < 25 years
- Caucasian /member of other ethnic group
- BMI < 27
- No history of GDM or glucose intolerance
- No family history of diabetes in first degree relative
- No history of GDM associated adverse pregnancy outcome

Average risk – Blood glucose testing is done at 24 – 28 weeks with one step or two step technique in pregnant females of Indian , Hispanic, Afro-American , Asian ethnic groups.

High risk – Blood glucose testing is done at the earliest, and if found normal, then repeated at 24 – 28 weeks or at any time when there are features of hyperglycemia in pregnant females having

- Obesity
- Family history of type 2 diabetes mellitus
- Previous history of GDM, impaired glucose intolerance , glycosuria

COMPLICATIONS OF GDM (Tracy L.Setji, et.al., 2005):
There are both fetal and maternal complications associated with GDM.

Fetal complications:
These include macrosomia , neonatal hypoglycemia , perinatal mortality, congenital malformation , hyperbilirubinemia , polycythemia, hypocalcaemia ,and respiratory distress syndrome. Neonatal hypoglycemia can occur within a few hours of delivery. This results from maternal hyperglycemia causing fetal hyperinsulinemia. Long term complications to the offspring include an increased risk of glucose intolerance , and obesity.

Maternal complications:
These include hypertension, preeclampsia ,and an increased risk of cesarean delivery.
More important is women with GDM have an increased risk of developing diabetes after pregnancy when compared to the general population , with a conversion rate of upto 3% per year.

SCREENING AND DIAGNOSIS:
A number of screening procedures and diagnostic criteria (American Diabetes Association (ADA) , World Health Organisation (WHO) ,National Diabetes Data group(NDDG) and Australian criteria) are being followed in the same as well as in different countries.

ADA (AMERICAN DIABETES ASSOCIATION) recommends SELECTIVE SCREENING in pregnant women having (Aruna Nigam, et.al., 2010)

1. Age > 25 yrs
2. Overweight before pregnancy
3. Ethnic group with high prevalence of GDM such as native Americans , Asians ,Hispanics and African-American women
4. History of abnormal glucose tolerance
5. History of poor obstetric outcome

ADA (Carpenter and Couston) Procedure (Seshiah V, et.al., 2009):
It is a TWO step procedure.
Step 1 : A 50 grams glucose challenge test (GCT) is used for screening without regard to the time of last meal or time of the day.
Step2: If 1 hour GCT value is > 140 mg/dl, 100 g ORAL GLUCOSE TOLERANCE TEST(OGTT) is recommended and plasma glucose is estimated at 0 , 1, 2, and 3 hr .
GDM is diagnosed if any of two or more values meet or exceed as shown in Table 1.

Table 1: Plasma glucose is estimated at 0 , 1, 2, and 3 hr

	ADA 100-g OGTT	ADA 75-g OGTT	WHO 75-g OGTT
Fasting (mg/dl)	95	95	126
1-hour(mg/dl)	180	180	---
2-hour(mg/dl)	155	155	140
3-hour (mg/dl)	140	---	---
For the ADA criteria, two or more of the values from either the 100 or 75-g OGTT must be met or exceeded to make the diagnosis of GDM. For the WHO criteria, one of the two values from the 75-g OGTT must be met or exceeded to make the diagnosis of GDM.			

When two step approach is employed , a glucose threshold value >140 mg/dl (7.8mmol/l) identifies approximately 80% of women with GDM , and the yield is further increased to 90% by using a cut-off value of > 130 mg/dl, but it has high false positive rate (7.2 mmol/l) (Tracy L.Setji, et.al., 2005).

WHO Procedure

WHO recommends UNIVERSAL SCREEING FOR GDM, which is used in many countries. Diagnosis is based on a 2hr 75 g OGTT. GDM is diagnosed if either Fasting plasma glucose is >126 mg/dl or 2 hr plasma glucose > 140 mg/dl (shown in Table 1) (Tracy L. Setji, et. al., 2005).

DRAWBACKS OF VARIOUS PROCEDURES (Seshiah V, et.al., 2009) :

ADA Procedure

1. The glycemic cutoff was originally validated against the future risk of these women developing diabetes and NOT on fetal outcome.
2. Further many women in community health centres are reluctant to undergo ADA procedure for following reasons
   a) number of blood samples drawn are many
      i) for screening and ii) for subsequent 3 hr OGTT to confirm the diagnosis (4 blood samples).
   b) they have to visit the antenatal clinic on two occasions – once for screening and again for diagnosis.

WHO Procedure

This criteria was also not based on the maternal and fetal outcome but probably the criteria was recommended for its EASY adaptability in clinical practice.

In INDIAN SCENARIO , screening is essential in all pregnant women as INDIANS have 11 fold increased risk of developing glucose intolerance during pregnancy as compared to Caucasian women. The pick up rate by WHO criteria is 3 times more than that of ADA criteria (Aruna Nigam, et.al., 2010) . So, universal screening is suitable for the Indian setting ,as recommended by WHO that serves as one step screening and diagnostic procedure , which is simple to perform besides being economical (V Seshiah, et.al., 2008).

GESTATIONAL WEEKS AT WHICH SCREENING IS RECOMMENDED

Insulin is detectable in the fetal pancreas as early as 9 weeks after conception. 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 (H Reiher, et.al.,1983 , Nahum GG, et.al.,2002). The priming of the fetal beta cells may account for the persistence of fetal hyperinsulinemia throughout pregnancy and the risk of accelerated fetal growth (Carpenter MW, et.al., 2001) , even when the mother enjoys good metabolic control in later pregnancy (R Schwartz, et.al., 1994). 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 (V Seshiah, et.al., 2008). 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 (Ben-Haroush, et.al.,2004, Jose L.Bartha, et.al.,2000). If the 2-h PG is > 200 mg/dl in the early weeks of pregnancy, she may be pre-GDM and A1c of > 6 is confirmatory (Balaji V,et.al.,2007). {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 again around 24th - 28th week and finally around 32nd – 34th week (Seshiah V, et.al.,2007, V Seshiah, et.al., 2008) .

MANAGEMENT

1. Patient Education
2. Medical Nutrition Therapy (MNT)
3. Insulin
4. Oral drugs

Patient Education:

It is essential educating women with GDM about the condition and its management. The compliance with treatment plan depends on the patient's understanding of

a. The implication of GDM for her baby and her self.
b. Dietary recommendations .
c. Self monitoring of blood glucose.
d. Self administration of insulin and adjustment of these insulin doses.
e. Identification and treatment of hypoglycemia (Patient & family members)
(Seshiah V, et.al., 2009).

Medical Nutrition Therapy (MNT)

The goals of MNT are to provide adequate nutrition for the mother and fetus, provides sufficient calories for appropriate maternal weight gain, maintain normoglycemia, and avoid ketosis (ADA , Diabetes Care 2003).

Insulin

Insulin is the pharmacological therapy that has most consistently been shown to reduce fetal morbidities when added to MNT. When maternal glucose levels are used, insulin therapy is recommended when MNT fails to maintain self-monitored glucose at the following levels (ADA, Diabetes Care 2003):

Fasting plasma glucose ≤ 105 mg/dl (5.8 mmol/l)
Or
1-h postprandial plasma glucose ≤155 mg/dl (8.6 mmol/l)
Or
2-h postprandial plasma glucose ≤130 mg/dl (7.2mmol/l)

TARGET BLOOD GLUCOSE LEVELS

In normal pregnancy , the mean plasma glucose (MPG)+SD value for fasting is 89 mg/dl, and 2 hour is 122 mg/dl. Thus maintenance of mean plasma glucose (MPG) level ~105mg/dl to 110 mg/dl is desirable for a good fetal outcome . This is possible if FPG and 2 hr postprandial peaks are ~ 90mg/dl and ~120mg/dl (Seshiah V, et.al., 2009).

INSULIN

It is ideal to use human insulins as they are least immunogenic,though insulin doesnot cross the placenta, 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 postprandial glucose value during pregnancy (V Seshiah, et.al., 2006). Lispro appears to be safe in pregnancy if started after 14 weeks of gestation and it is the first analogue to get category B approval by USFDA (Tracy L.Setji, et.al., 2005) and Aspart has also been found to be safe and effective in management of GDM (V Seshiah, et.al., 2006).

ORAL ANTI-DIABETIC DRUGS:

GLYBURIDE

Reports have shown good fetal outcome in GDM women who were on glyburide (micronized 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 control goals on MNT. Treatment with either agent resulted in similar perinatal outcomes. All patients were beyond the first trimester of pregnancy at the initiation of therapy (Langer O, et.al., 2000). However ,further studies regarding use of glyburide are needed in a larger patient population to establish its safety (TracyL.Setji,et.al.,2005).

METFORMIN

A randomized controlled study found that in women with GDM , metformin (alone or with insulin) was not associated with increased perinatal complications as compared with insulin (Janet A.Rowan, et.al., 2008). Metfromin has been found to be useful in women with polycystic ovarian disease (PCOD) who failed to conceive (Misra S, et.al.,2004 , Daniela J. Jakubowicz et.al., 2002). Continuing this drug after conception is still a controversy, but there are few studies favouring continuation of metformin throughout pregnancy in these women (Daniela J . Jakubowicz, et.al.,2002).
However , more studies are required before routinely recommending oral anti-diabetic agents during pregnancy.

TIMING OF DELIVERY

Most obstetricians 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 due to unfavourable conditions of the cervix but this also has to be balanced against the poorly defined and predictable risk of late intrauterine 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 . A neonatologist support at the time of delivery is advisable (V Seshiah, et.al, 2006).

FOLLOW UP OF GDM

Gestational diabetic women require follow up. Glucose tolerance test with 75 g oral glucose is performed after 6 weeks of delivery and if necessary repeat 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 (V Seshiah, et.al, 2006).

RECURRENCE OF GDM

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 (V Seshiah, et.al., 2006).

COUNSELLING

Women with GDM have to receive counselling with regard to their increased risk of developing permanent diabetes. Indian women with GDM have a high risk of developing diabetes (especially type 2 diabetes mellitus), and metabolic syndrome at a comparatively younger age. They should be made aware of the symptoms of hyperglycemia and advice should be given about the importance of healthy eating habits and exercise patterns for maintaining ideal body weight.

Contraceptive advice and counselling about planning future pregnancies should be given (Seshiah V, et.al., 2009).

CONCLUSION

GDM is a common medical problem that results from an increased severity of insulin resistance as well as an impairment of the compensatory increase in insulin secretion. Pregnancy, in essence, serves as a metabolic stress test and uncovers underlying insulin resistance and beta-cell dysfunction. GDM is associated with a variety of maternal and fetal complications, most notably macrosomia.

WHO recommends universal screening of all pregnant women for GDM.

Majority of guidelines suggest screening between 24-28 weeks but few studies suggest screening to diagnose GDM in the first trimester itself as early detection and care , results in a better fetal outcome. In Indian setting , one step procedure recommended by WHO(75g OGTT) is feasible in terms of better detection rate , saves time, limits cost due to repeated visits to health centre and reduces repeated invasive sampling.

GDM women have a high risk of developing diabetes in the future . They are ideal group to be targeted for lifesylte modifications and pharmacologic intervention inorder to delay or postpone the onset of overt diabetes. Offspring of women with GDM should be followed carefully for the development of obesity and / or abnormalities of glucose tolerance .

The maternal 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, impaired gluose tolerance(IGT) and diabetes in the offspring , as the preventive medicine starts before birth .

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