

## Unveiling the Controversies in Gestational Diabetes Mellitus

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### Abstract

Gestational Diabetes Mellitus (GDM) constitutes approximately 90% of diabetes cases in pregnant women. Increasing age, obesity, family history of diabetes, past history of abnormal glucose tolerance are the important risk factors for development of GDM. Both maternal and fetal complications can arise due to GDM. Urinary tract infection, pre-eclampsia, pre term labour and post-partum haemorrhage are the important maternal complications which results due to GBM. Common fetal complications are spontaneous abortion, Intra uterine growth retardation (IUGR), neonatal hypoglycaemia, shoulder dystocia and macro-osmia. All pregnant women should undergo screening for glucose intolerance. The usual recommendation for screening is between 24 and 28 weeks of gestation. Lifestyle modification and medical nutrition therapy (MNT) remains the starting point of diabetic therapy in pregnancy. When it fails insulin therapy is initiated. Oral anti diabetic drugs like metformin and glyburide may also be used in settings where insulin therapy is not feasible due to poor patient compliance or unavailability. Maintenance of Mean Plasma Glucose (MPG) level ~105 mg% is ideal for good fetal outcome. This is possible if FPG and post prandial peaks are around 90 mg/dl and 120 mg/dl respectively. GDM is a serious disorder complicating pregnancy, its early screening and detection is important in commencement of treatment to prevent adverse maternal and fetal outcomes.

**Keywords:** Gestational Diabetes Mellitus (GDM); Mean Plasma Glucose (MPG); Intra Uterine Growth Retardation (IUGR)

### Introduction

Diabetes is one of the most common medical disorders that complicate pregnancy. Its incidence among women of reproductive age is rising globally. As a result of that the prevalence of overt diabetes in pregnancy and gestational diabetes mellitus (GDM) has also risen. Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance that occurs during pregnancy. Approximately 90% of diabetes cases in pregnant women are considered gestational diabetes mellitus (GDM). The overall incidence of GDM is 5 - 7% of all pregnancies [1,2]. The incidence is 5% in the United States, and 3.8 - 17.9% in different parts of India [3]. Diabetes in pregnancy is associated with an increased incidence of undesirable outcomes, for both mother and infant, if the glycemic control during pregnancy is not adequate [4].

### Pathophysiology

The normal pregnancy is accompanied by insulin resistance. It is mediated primarily by secretion of certain hormones from placenta that increases blood glucose levels. This includes growth hormone, corticotropin-releasing hormone, placental lactogen, and

progesterone. So, in those women whose pancreatic function is insufficient to overcome the insulin resistance associated with the pregnant state, GDM occurs [5]. Obesity and overweight are nearly frequent findings among women in their childbearing years. Obesity is also associated with insulin resistance and is considered to be a state of chronic inflammation in which inflammatory markers are produced in excess to systemic circulation. These inflammatory markers influence alterations in post-receptor insulin signalling resulting in increased insulin resistance [3,5].

### Risk factors for GDM

Women with following features are at risk of developing GDM [4,6]:

1. Age > 33 years of age.
2. Overweight or obesity.
3. History of diabetes in first degree relative.
4. Past history of abnormal glucose tolerance.
5. Past history of poor obstetric outcome.
6. Past history of large sized baby.

### Complications of GDM

There can be both fetal and maternal complications as a result of hyperglycemia.

#### Maternal

1. UTI
2. Pre-eclampsia
3. Pre term delivery
4. Post-partum haemorrhage

Women who are diagnosed with GDM are at high risk of developing diabetes mellitus later in life. Approximately 10% of women with GDM have diabetes mellitus soon after delivery. The rest have 20 - 60% develop diabetes mellitus at rates within 5 - 10 years after the index pregnancy in the absence of specific interventions to reduce their risk of diabetes mellitus [6].

#### Fetal

1. Spontaneous abortion
2. IUGR
3. Neonatal hypoglycaemia
4. Shoulder dystocia
5. Macro-osmia
6. Jaundice
7. Polycythaemia.

### Screening and diagnosis of GDM

All the pregnant women should undergo screening for glucose intolerance. The usual recommendation for screening is between 24 and 28 weeks of gestation. Fasting blood glucose levels are tested then 75g of oral glucose is given and blood glucose levels are again tested after at 1 hour and 2 hour post glucose challenge. 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 16<sup>th</sup> week of gestation. If found negative at this time, the screening test is to be performed again around 24<sup>th</sup> - 28<sup>th</sup> week and finally around 32<sup>nd</sup> - 34<sup>th</sup> week [7].

Various criteria for diagnosing GDM are shown in table 1 [7-10].

75 gram oral glucose tolerance values	ADA	NICE 2015	IADPSG	WHO 2013	DIPSI
Fasting	92 mg%	≥ 100 mg%	92 mg%	92 - 125 mg%	
1 hour	180 mg%		180 mg%	≥ 180 mg%	
2 hour	153 mg%	≥ 140 mg%	153 mg%	153 to 199 mg%	≥ 140 mg%

**Table 1**

## Management

Lifestyle modification and medical nutrition therapy (MNT) remains the starting point of diabetic therapy in pregnancy [11]. However, in pregnancy, rapid control of blood glucose levels is required. Approximately 30 Kcal/kg bodyweight or an increment of 300 kcal/day above the basal requirement is needed. In women who have higher BMI the total calories may be restricted as 25 kcal/kg for women with a BMI of 26 to 29, and 15 - 20 kcal/kg for women with a BMI above 30. 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. But if a trial of MNT fails to achieve glycemic control within a week or less, diabetic therapy need to be escalated. Insulin is the drug of choice in majority of women with GDM [8,9]. Insulins such as regular, lispro, aspart, and neutral protamine hagedorn (NPH) are well-studied in pregnancy and regarded as safe and effective. Insulin glargine is a long acting analogue and may exacerbate periods of maternal hypoglycaemia [14]. Insulin detemir is safe and comparable to NPH insulin in pregnancy [15]. As of now among long acting insulins, insulin glargine has been assigned as category "C".

## Insulin therapy

A basal bolus regime with three shots of short acting insulin just before meals and a long acting insulin (Detemir or NPH) can be started for control of blood glucose levels. Adjusting insulin dose is simpler with self-monitoring of blood glucose (SMBG) four times a day. It is important to remember that insulin requirement increases with pregnancy, if it does not happen as expected, it can be a cause of concern, and one should rule out IUGR, poor placental growth, and impending intrauterine death.

## Role of oral anti diabetic drugs in pregnancy

Many Randomised controlled trials (RCT) support the efficacy and short-term safety of metformin and glyburide for the treatment of GDM, both agents cross the placenta in variable extents, long-term safety data are not yet available for any oral agent. The Endocrine society (USA) has suggested that glyburide is suitable alternative to insulin therapy for glycemic control in women with gestational diabetes who fail to achieve sufficient glycemic control after a 1-week trial of MNT and lifestyle modification. However, for the women with a diagnosis of GDM before 25-weeks gestation and for those women with fasting plasma glucose > 110 mg/dl (6.1 mmol/L), in that case insulin therapy is preferred [16]. Starting dose of glyburide is 2.5 mg once daily and can be increased up to a maximum of 20 mg/day. The usual starting dose of metformin is 500 - 1000 mg/ day, which can be increased gradually up to a maximum dose of 2500 mg/day. The use of OADs in pregnancies is not recommended by the American Diabetes Association (ADA), whereas UK National Institute for Health and Care Excellence (NICE) guidelines considers metformin and glyburide safe in pregnancy and lactation. In Scotland, the Scottish Intercollegiate Guidelines Network (SIGN publication no. 116; 2010) suggested that metformin or glyburide may be considered as initial pharmacological, glucose-lowering treatment in women with gestational diabetes [17]. No OAD is approved by the US Food and Drug administration (FDA) for treatment of diabetes in pregnancy [7,8]. National guidelines for the management of GDM 2014 (Govt. Of India) does not approve the use of OADs.

## Target blood glucose levels [9,10]

Maintenance of Mean Plasma Glucose (MPG) level ~105 mg% is ideal for good fetal outcome. 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). Table 2 shows glycemic targets according to different guidelines in pregnancy.

	NICE	ADA	DIPSI
Fasting	< 5.3 mmol/l 95 mg/dl	< 95 mg/dl	< 90 mg/dl
One hour Post prandial	< 7.8 mmol/l 140 mg/dl	< 140 mg/dl	
Or 2 hour post prandial	< 6.4 mmol/l 115 mg/dl	< 120 mg/dl	< 120 mg/dl

**Table 2:** Glycemic targets in pregnancy.

**Management during labor and postpartum**

For taking decision on timing and mode of delivery in women with GDM, there is no general agreement. However, induction of labour is beneficial in terms of avoiding obstetric complications related to foetal overgrowth [18]. The ACOG recommend considering elective Caesarean delivery if the estimated foetal weight more than 4.5 kg to prevent birth trauma [19]. Insulin requirement during labor is generally decreased because of increased physical work and also because women may remain fasting for long time. Some women may also need glucose infusion to prevent ketosis [20].

After delivery, most of the women return back to their previous pre-gestational glycemic levels within one week. However, few women may continue to have hyperglycaemia possibly representing those women who were undiagnosed with overt diabetes before pregnancy [21]. For this reason the Endocrine Society recommends to keep checking for glucose level until 72h following delivery to rule out continuing hyperglycaemia. Treatment is then justified on individual basis if Diabetes mellitus type 2 (T2DM) is diagnosed or, if not, it is recommended to perform a 2-h 75g OGTT 6 - 12 wk following delivery to test for glucose intolerance or T2DM.

**Prevention of T2DM in women with prior history of GDM**

The Diabetes Prevention Program (DPP) study shows that intensive lifestyle modification and metformin at a dose of 850 mg twice daily, reduced the incidence of T2DM by 58% and 31% respectively in women who had GDM [22]. This has been further confirmed in the long-term follow-up of the original DPP study: DPP Outcomes Study (DPPOS) Obese women have a greater risk of GDM than women with normal body weight [23].

**Conclusion**

GDM is a serious disorder complicating pregnancy. Several maternal and foetal comorbidities are associated with GDM. Its early screening and detection is important in commencement of treatment to prevent adverse maternal and fetal outcomes. It involves synergy in the role of obstetrician as well as physician for achieving euglycemic goals during pregnancy. In the long-term GDM carries a major risk of developing T2DM, metabolic syndrome later in life for the mother. There is still no universal consensus for glycemic goals and risk assessment. It is prudent that well-designed RCTs are required in the future to ascertain optimal glycemic targets, and appropriate monitoring of women to assess their risk status for later development of T2DM and CVD.

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