CHAPTER

# 179

# Hyperglycemia in Pregnancy

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## INTRODUCTION

Hyperglycemia is one of the most common medical disorders seen in women enco during pregnancy. The International Diabetes Federation (IDF) estimates that one in six live births (16.8%) are to women with some form of hyperglycemia in pregnancy. Of them, 84% are gestational diabetes mellitus (GDM), while 16% may be due to diabetes in pregnancy (either pre- existing diabetes—type 1 or type 2—which antedates pregnancy or is first identified during testing in the index pregnancy.[1]

The GDM prevalence correspondences with the prevalence of impaired glucose tolerance (IGT) and type 2 diabetes mellitus (T2DM) in any given population. Unfortunately, the age of onset of pre-diabetes and diabetes is declining, whereas childbearing age is increasing. Moreover, overweight and obesity is increasing in women of reproductive age; thus, more women are entering pregnancy have risk factors that make them vulnerable to hyperglycemia during pregnancy.

GDM is associated with a higher incidence of cesarean deliveries, shoulder dystocia, birth trauma, hypertensive disorders of pregnancy (including pre-eclampsia), and these women are at higher risk for development of T2DM. The perinatal and neonatal morbidities also increase; the latter include macrosomia, neonatal hypoglycemia, birth injury, polycythemia, and hyperbilirubinemia. Moreover, offspring in utero, if exposed to maternal hyperglycemia may remain at higher risks for childhood obesity and diabetes later in life. The relevance of GDM as a priority for maternal health and its impact on the future burden of noncommunicable diseases is no longer in doubt.[2] By early detection, aggressive management and adequate education, we will be protecting two generations, one the mother and other is offspring of diabetic mother. Thus, keeping uniformity in diagnosis criteria and treatment strategy across is the need of the hour.

Definition: The earlier GDM definition was "any degree of glucose intolerance with onset or first recognition during pregnancy." [3]

This definition doesn't differentiate between clinically pre-existing T2DM and rarely T1DM, which get detected during screening of hyperglycemia in pregnancy. Therefore, hyperglycemia first detected at any time during pregnancy should be classified either as diabetes mellitus in pregnancy (DIP) or GDM.[4]

## CLASSIFICATION

### Diabetes in pregnancy (DIP)

DIP may either have been pre-existing diabetes (type 1 or type 2) antedating pregnancy, or diabetes first diagnosed during pregnancy (Figures 1 & 2)[2]. Women with pre-existing hyperglycemia at conception and embryogenesis, increases the vulnerability and risk of complications in women. Similarly, any undiagnosed diabetes antedating pregnancy may also have undiagnosed diabetic complications including retinopathy and nephropathy, which significantly increases pregnancy risks[5] Moreover, hyperglycemia during the critical period of organogenesis may lead to a high risk of congenital anomalies and spontaneous abortions. Additionally, Macrosomia, shoulder dystocia, obstructed labor, neonatal hypoglycemia, risk of neurological damage, risk of exacerbation of retinopathy or nephropathy also

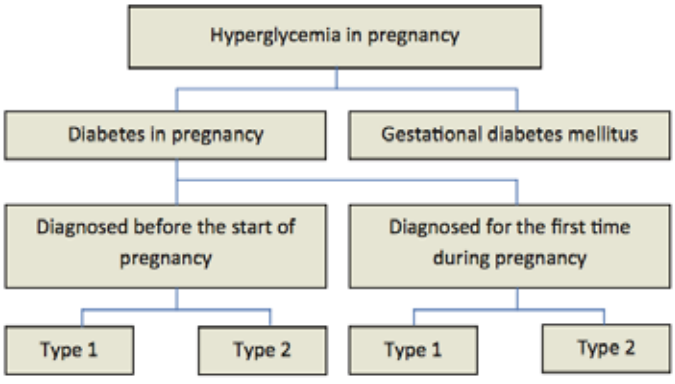


**Fig. 1: Types of hyperglycemia in pregnancy**

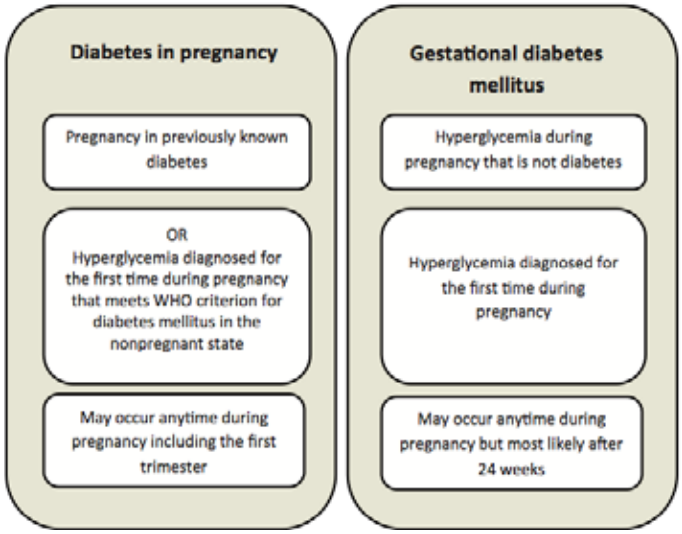


**Fig. 2: The difference between diabetes in pregnancy and gestational diabetes mellitus**

increases in women with DIP. Thus, meticulous blood glucose control before conception and then throughout pregnancy is recommended. Compared with gestational diabetes, DIP is more likely to be detected as early as the first trimester provided appropriate testing is undertaken.

## Gestational diabetes mellitus

When hyperglycemia detected during routine testing in pregnancy (generally between 24 and 28 weeks) does not meet the criteria of DIP it is called GDM. GDM implies a relatively milder form of hyperglycemia compared with that of DIP, but is also associated with a increased risk of poor pregnancy outcome and future risk of diabetes and cardiovascular disease, and should be managed judiciously.

GDM prevalence has been reported to vary between 1%–28% in different region globally, while the International Diabetes Federation (IDF) estimates that one in six live births (16.8%) are to women with some form of hyperglycemia in pregnancy; 16% of these may be due to DIP, while the majority (84%) is related to GDM.[1]

A south Indian study showed the prevalence to be 13.9%. It was 17.8% in Urban, 13.8% in semiurban and 9.9% in rural Indian women. Among the women with GDM, 12.4% were detected within 16 weeks of pregnancy, 23% between 17 and 23 weeks, and the remaining 64.6% at more than 24 weeks of pregnancy. The mean age of the pregnant women screened in the urban, semi-urban, and rural areas was 23.7± 3.55 years, 23.4±3.30 years, and 22.5±3.09 years, respectively. There was a consistent increase in the prevalence of GDM in all 3 areas as BMI increased, and the trend was statistically significant (P <0.0001).[6]

Among the women with GDM, the highest prevalence was observed in women with a BMI greater than 25, with 28.4% in the urban area, 23.8% in the semi-urban area, and 16.1% in the rural area. A positive family history of diabetes mellitus was present in 25% of the women with GDM in the urban, 19.2% in the semi-urban, and 14.1% in the rural area. There was a significant association (P<0.001) between family history of diabetes mellitus and the occurrence of GDM among pregnant women. Based on univariate analysis, author observed in all 3 areas that age greater than 25 years, BMI greater than 25, and family history of diabetes were significantly associated with the prevalence of GDM in India. Based on multiple logistic regression analysis taking all 3 areas into consideration, family history and BMI greater than 25 were found to have a significant independent association (P<0.001) with GDM.[6]

## Risk Factors

Indians have higher risk of developing GDM v/s Caucasians. Other risk factors are: obesity older age, multi-parity, excessive weight gain during pregnancy, short stature, polycystic ovarian syndrome (PCOS), family history of diabetes mellitus in first degree relatives, a past history of abortion, fetal loss, macrosomia, GDM, pre-eclampsia, and multifetal pregnancy.[7]

## Pathophysiology

Mother during pregnancy, eats intermittently, while fetus gets feed continuously. This is being mediated through secretion of hormones like human placental lactogen (HPL), estrogen, progesterone etc with complex interactions of the feto-placental- maternal unit, and metabolic mediators that create insulin resistance and modify maternal carbohydrate, lipid, and amino acid metabolism to ensure sufficient nutrient supply to the fetus. Maternal insulin secretion increases due to increasing insulin resistance, to maintain euglycemia. These is achieved at the cost of higher maternal insulin level. While fasting glucose levels remain lower than non-pregnant fasting levels. Insulin resistance continuously increases with advancing pregnancy. Till the maternal beta cells continues to increase insulin production and secretion, hyperglycemia is prevented. When this capacity is decompensated due to rising insulin resistance, maternal hyperglycemia ensues. Thus, it is said that pregnancy is a stress test for beta cells of pancreas.

## Fetal implications

An abnormal intrauterine environment has consequences in later life mediated through epigenetic changes. This phenomenon is known as developmental programming. Abnormal metabolic environment of the mother with hyperglycemia may affect certain developing fetal tissues and organs, eventually leading to permanent long-term functional implications in adult life. The fetal tissues most likely to be affected are neural cells, pancreatic beta cells, muscle cells and adipocytes. Early exposure to the aberrant fuel mixture in the first trimester may cause intrauterine growth restriction and organ malformation, described by Freinkel as "fuel-mediated teratogenesis". During the second trimester, at the time of brain development and differentiation, behavioral, intellectual, or psychological damage may occur. During the third trimester, abnormal proliferation of fetal adipocytes and muscle cells, together with hyperplasia of pancreatic beta cells and neuroendocrine cells may be responsible for the development of obesity, hypertension, and T2DM mellitus later in life.[8]

## Diagnosis of GDM

International Association of Diabetes in Pregnancy Study Group (IADPSG, 2010) and WHO (2013) recommended that the diagnosis of GDM should be made through single-step 75-g OGTT when one or more of the following results are observed during routine testing specifically between 24 and 28 weeks of pregnancy or at any other time during the course of pregnancy:

a. Fasting plasma glucose 92–125 mg/dL;

b. 1-hour post 75-g oral glucose load ≥ 180 mg/dL;

c. 2-hour post 75-g oral glucose load 153–199 mg/dL

## DIPSI (Diabetes In Pregnancy Study group in India) & Government of India Guidelines

DIPSI and Government of India recommend universal screening for GDM at their initial prenatal visit, using

standard diagnostic criteria, 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 2DM.[9]

DIPSI recommends that in the antenatal clinic, a pregnant woman after undergoing preliminary clinical examination, has to be given a 75 g oral glucose load, irrespective of whether she is in the fasting or nonfasting state and 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-hour PG is ≥ 140 mg/dl. This test serves as both screening and diagnostic procedure. DIPSI has also recommended in their earlier publication, that any 2hr 75gm OGTT value < 120mg% is normal, but blood glucose between 120 & 140 mg% should also be classified as GGI (Gestational Glucose Intolerance) and should also be treated.[10]

### Management & Targets In GDM

The 5th International Workshop Conference on GDM made recommendations relating to targets for glycaemia during GDM pregnancy, and the potential role of fetal growth targets. The workshop recommended maintaining capillary blood glucose at <96 mg /dl in the fasting state, <140 mg /dL) at 1 h and <120 mg/ Dl at 2 h after starting a meal. These targets were based on the then knowledge of normal glycaemia in pregnancy and the outcomes of the ACHOIS study. They commented that data from controlled trials of lower versus higher targets were lacking.[11]

### Monitoring Of Glycaemia in GDM

Close monitoring and treatment of GDM are important to the long-term health of a pregnant woman and her baby. Women with GDM should monitor Fasting, 2hr Post Breakfast, 2hr Post Lunch and 2hr post-dinner regularly. Baseline and interval hemoglobin A1c levels during treatment are helpful, particularly in women who have fasting hyperglycemia.

## MANAGEMENT

### Medical Nutrition Therapy

The initial treatment for GDM continues to be diet and exercise. The nutritional counseling, if possible should be given by a registered dietitian, with individualization of the nutrition plan based on height and weight. For normal-weight women (BMI: 20-25 kg/m$^2$) 30 kcal/kg should be prescribed; for overweight and obese women (BMI > 24-34 kg/m$^2$) calories should be restricted to 25 kcal/kg, and for morbidly obese women (BMI > 34 kg/m$^2$) calories should be restricted to 20 kcal/kg or less. Moses and colleagues[12] showed that a low-glycemic diet decreased the need and timing for insulin in GDM women. The Fifth International Workshop-Conference on GDM recommends a relatively small gain during pregnancy of 7 kg or more for obese women (BMI ≥ 30 kg/m$^2$) and a proportionally greater weight gain (up to 18 kg ) for underweight women (BMI < 18.5 kg/m$^2$) at the onset of pregnancy. However, there are no data on optimal weight gain for women with GDM.[13,14]

### Role of Exercise

Exercise plays a major role in both prevention and management of GDM. Experts at the Third International Workshop-Conference on Gestational Diabetes Mellitus[15] suggested that active women who have GDM may continue moderate exercise. Active lifestyle program in a group of inherently inactive pregnant woman may not only improve glycemic control acutely, but may reduce the risk or delay the onset of developing diabetes. Artal and colleagues[16] provided exercise guideline for women with GDM as below:

- Rests for 30 min before breakfast, lunch, and dinner, and monitors fetal activity.
- Monitors fasting and 2-hr postprandial blood glucose by glucometer.
- If fetal activity & glucose level are acceptable, women should exercise for 20 to 30 min, keeping heart rate <140 beats/ minute
- Then rests for 30 min and counts fetal movements
- If uterine contractions become less, one should report obstetrician
- Maintain records of blood glucose, food intake, exercise and fetal movements.
- After 32 weeks gestation, non-stress testing to be done weekly;

## PHARMACOTHERAPY

### Insulin Therapy

Pharmacologic therapy is instituted once diet and exercise fail to achieve the glycemic goals.. Traditionally, insulin has been the drug of choice because of its safety in pregnancy, lack of significant transplacental passage, and history of its use. Most women can be treated as outpatients. Insulin dose should be individualized. The recommended initial insulin dose for pregnancy is based on maternal weight and can be calculated by the following guidelines to determine total daily insulin needs: 0.7 U/kg actual body weight in the first trimester, 0.8 U/kg actual body weight in the second trimester, and 1.0 U/kg actual body weight in the third trimester. However, because women with GDM have varying degrees of severity, in practice, insulin is started at 0.7 U/kg actual body weight to prevent hypoglycemia at home. Clinical judgment and experience assist in the selection of the starting dose of insulin. Once the total daily insulin dose is calculated, two-thirds of the daily dose is given before breakfast, divided into two-thirds Neutral Protamine Hagedorn (NPH) insulin and one-third regular insulin, and the remaining one-third of the daily dose is divided into half regular insulin before dinner and half NPH insulin at bedtime. Being GDM a postprandial hyperglycemic state, short-acting or rapid acting insulin can a be used and is best dosed with each meal in place of the twice-daily regular insulin.[17]

Our own data has shown that 56% of women with GDM may require insulin to achieve their goals. Mean Insulin

dose required in GDM women was 0.4 U/Kg/day. In the basal-bolus dose regimen, dose requirement our population required lowest dose during breakfast, higher in lunch (p=0.0002) while highest dose of short acting insulin with dinner (p<0.0001). The insulin dose was directly proportional to FBG (p<0.0001) and pre pregnancy weight (p<0.008), but it couldn't be correlated to Age, Pre Pregnancy BMI.[18] For many years, fast-acting (regular) insulin, and intermediate-acting (isophane) insulin have been the preferred insulins for the treatment of GDM. Human insulin does not normally cross the placenta, though antibody bound animal insulin has been reported to do so. However, it has been shown by Jovanovic that it is maternal glucose control, rather than maternal anti-insulin antibody levels which influence birth weight. Lispro, Aspart & Levemir Long acting analogue, have been already approved by US FDA as class B drug for its use in pregnancy. Levemir has been recently approved by USA FDA for its use in pregnancy as class B drug.[19]

There are papers available in favour of use of glargine in pregnancy, but it, has not been approved yet.

## ROLE OF ORAL ANTIDIABETIC AGENT

Traditionally, insulin therapy has been considered the gold standard for management because of its efficacy in achieving tight glucose control and the fact that it does not cross the placenta. Insulin is, however, is invasive treatment. Insulin therapy involves daily injections, and patient compliance is often suboptimal. Clinicians and women with diabetes would prefer tablets rather then multiple injections, if safety data of SU & Metformin become available in future, along with approval from drug controller authorities and global recommendation.

### Glibenclamide

Importantly, glibenclamide is currently the only sulphonylurea that has been investigated with a randomised controlled study. There are conflicting studies regarding transfer of glyburide (Glibenclamide) across placenta. The in vitro studies have shown minimal transfer.[20] A recent in vivo study has shown transfer at term but mentions that glyburide appears safe to fetus at maternal doses up to 20 mg/d and that the glyburide concentration-response relationship remains uncertain.[21] NICE has suggested it may offer an alternative to insulin in selected patients with GDM, where insulin therapy is either declined or poorly tolerated. Currently ADA & DIPSI did not recommend use of SU in GDM or Pre GDM women

### Metformin

Metformin does cross placenta but targets insulin resistance & thus, it does not cause hypoglycaemia. There is no convincing evidence for teratogenicity with metformin. The large-scale randomized trial, metformin in gestational diabetes (MiG) study looked at the effects on perinatal complications with metformin use in the second and third trimester, with mothers suffering from GDM. They found no difference in primary composite end-points between metformin and insulin groups. There was a significantly increased rate of premature deliveries, but these were noted to be spontaneous, rather than iatrogenic in response to complications, and resulted in the delivery of healthy infants. Moreover, over half the metformin treated group were able to maintain glycaemic control on OADs alone, and mothers found it preferential to insulin therapy.[22] NICE has advocated the use of metformin as an adjunct or alternative to insulin in the pre-conceptual and gestational period, in both GDM and pre-existing T2DM, whilst considering the risk/benefit ratio of treatment with the OAD, and hyperglycaemia.[23]

### Role of Other Antidiabetic drugs in GDM

Scanty data is available for use of Acarbose in pregnancy Because of the lack of human data regarding acarbose in pregnancy, the assessment of risk is impossible, so it is not recommended. Glitazones. Gliptins, Gliflozins & GLP1 analogues are contraindicated in pregnancy.

### Intrapartum Management

Most women with GDM will not need any insulin during labour or LSCS. Blood glucose should be kept between 90mg% to 120mg% during this period, to avoid neonatal hypoglycemia. If blood glucose is higher than these values, then patient need to take Insulin, either by infusion or by subcutaneous route on individual basis.

## CONCLUSION

Prevalence of Gestational Diabetes Mellitus is increasing in the same proportion as that of Type 2 DM or Impaired Glucose Tolerance, especially in India. Screening of GDM is an opportunity to diagnose those women who are likely to develop diabetes in future. Moreover, good control of intrauterine metabolic milieu is expected to prevent long term metabolic complications in adult life of offspring of GDM mother. Thus, two generations are being taken care, by detecting a GDM women. Apart from diet and exercise, insulin remains the drug of choice. Newer rapid acting insulin analogues are more physiological in their action, to get better postprandial control. Oral antidiabetic drugs, like sulphonylurea, is not recommended for its use in GDM or PreGDM women. Metformin, if being used for PCOD, may be continued during pregnancy. In rare circumstances, it may be used in combination with insulin, as an insulin sensitizer.

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