

# Gestational Diabetes Mellitus: Challenges in Diagnosis and Management

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## ABSTRACT

Diabetes mellitus is a chronic illness that requires continuing medical care and ongoing patient self-management education and support to prevent acute complications and to reduce the long-term complications. Moderate-to-severe maternal hyperglycemia in pregnancy has unique diabetes-related risks to mother and her unborn baby. So, gestational diabetes mellitus (GDM) is a carbohydrate intolerance that has been diagnosed for the first time during pregnancy. Approximately, 7% of pregnancies are affected by GDM.

Patients with GDM are at higher risk for excessive weight gain, preeclampsia, and cesarean sections. Infants born to mothers with GDM are at higher risk for macrosomia, birth trauma, and shoulder dystocia. After delivery, these infants have a higher risk of developing hypoglycemia, hypocalcemia, hyperbilirubinemia, respiratory distress syndrome, polycythemia and subsequent obesity, and type II diabetes.

The management of GDM is very important, and its management remains a challenge for obstetricians and endocrinologists. Medical nutritional therapy (MNT) is the initial and most common therapy that suffices for GDM. Pharmacological therapy becomes necessary, and the treatment of choice is human insulin. Oral hypoglycemic agents have also reached the high tables in the management of GDM. Glyburide and metformin have been found to be safe, effective, and economical for the treatment of gestational diabetes.

**Keywords:** Gestational diabetes mellitus, Glucose intolerance, Insulin, Medical nutritional therapy, Oral hypoglycemic agents.

**How to cite this article:** Garg R, Roy P, Agrawal P, Gautam A, Goel H, Hokabaj S, Malhotra N. Gestational Diabetes Mellitus: Challenges in Diagnosis and Management. *J South Asian Feder Obst Gynae* 2018;10(1):54-60.

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**Source of support:** Nil

**Conflict of interest:** None

**Date of received:** 15 January 2018

**Date of acceptance:** 25 February 2018

**Date of publication:** May 2018

## INTRODUCTION

Diabetes mellitus is a chronic illness that requires continuing medical care and ongoing patient self-management education and support to prevent acute complications and to reduce the long-term complications. Gestational diabetes mellitus, by definition, is any degree of glucose intolerance with onset or first recognition during pregnancy.<sup>1</sup> Gestational diabetes mellitus affects roughly 7% of pregnancies with an incidence of more than 200,000 cases per year.<sup>2</sup> It contributes to about 90% of diabetes complicating pregnancy.<sup>3</sup> It imposes risks for both mother and fetus, some of which continues throughout the life of mother and child. Immediate maternal complications include preeclampsia, need for cesarean section, and polyhydramnios.<sup>4</sup> Complications in the baby include hyperinsulinemia, macrosomia, shoulder dystocia, neonatal hypoglycemia, and respiratory distress syndrome.

Women with GDM have 40 to 60% chance of developing diabetes mellitus over 5 to 10 years after pregnancy.<sup>1</sup> Gestational diabetes mellitus also increases the risk of obesity and glucose intolerance in the offspring.<sup>5</sup> It is therefore, an important public health issue that has major repercussions for both mother and offspring. Detection of GDM thus provides a window of opportunity to intervene and reduce adverse perinatal outcomes.<sup>6</sup>

## Epidemiology

The prevalence of GDM depends on which population was being studied and what screening strategies and diagnostic criteria were used. The prevalence in the United Kingdom, USA, and among European countries was estimated to be 5, 3 to 7, and 2 to 6% respectively. Higher prevalence of GDM was noted in African, Asian, Indian, and Hispanic women.<sup>7</sup>

The International Diabetes Federation estimates that as of 2015, 16.2% of women with live births had some form

of hyperglycemia in pregnancy, 85% of which were due to gestational diabetes.<sup>8</sup> Asian women are more prone to develop GDM than European women, and Indian women have 11-fold increased risk of developing glucose intolerance in pregnancy compared with Caucasian women.<sup>9</sup> In the Indian context, the prevalence of GDM is steadily increasing from 2% in 1982 to 7.2% in 1991 and which has doubled to 16.55% in 2002. In 2013, 6 million women in India had some form of hyperglycemia in pregnancy, of which 90% were GDM.<sup>10,11</sup> Gestational diabetes mellitus is usually asymptomatic and is most commonly diagnosed by routine screening during pregnancy. Unfortunately, there is little agreement on the best screening and diagnostic tests for GDM.

It is estimated that 4 million women are affected by GDM in India,<sup>12</sup> at any given time point. The prevalence of gestational diabetes has been reported to range from 3.8% in Kashmir<sup>13</sup> to 6.9% in Mysore,<sup>14</sup> 9.5% in western India,<sup>15</sup> and 17.9% in Tamil Nadu.<sup>4</sup> In more recent studies, using different criteria, prevalence rate as high

as 35% from Punjab<sup>16</sup> and 41% from Lucknow<sup>17</sup> has been reported (Fig. 1). Studies on prevalence of GDM in India are summarized in Table 1.

## SCREENING

The first screening test for GDM, proposed in 1973, consisted of 1-hour 50 gm oral glucose tolerance test (OGTT).<sup>18</sup> While some guidelines recommend universal screening, others exempt those patients who are categorized as low risk. Evidence suggests that universal screening improves pregnancy outcomes compared with selective screening (Table 2).<sup>19</sup>

Although some experts recommend against screening low-risk patients routinely,<sup>2</sup> selective screening could miss approximately 4% of patients with GDM.<sup>22</sup> Pregnant women with high risk factors for GDM should be screened for GDM as soon as possible, preferably during their first antenatal visit. If negative, they should be retested at the beginning of their third trimester between 24 and 28 weeks of gestation. When universal screening

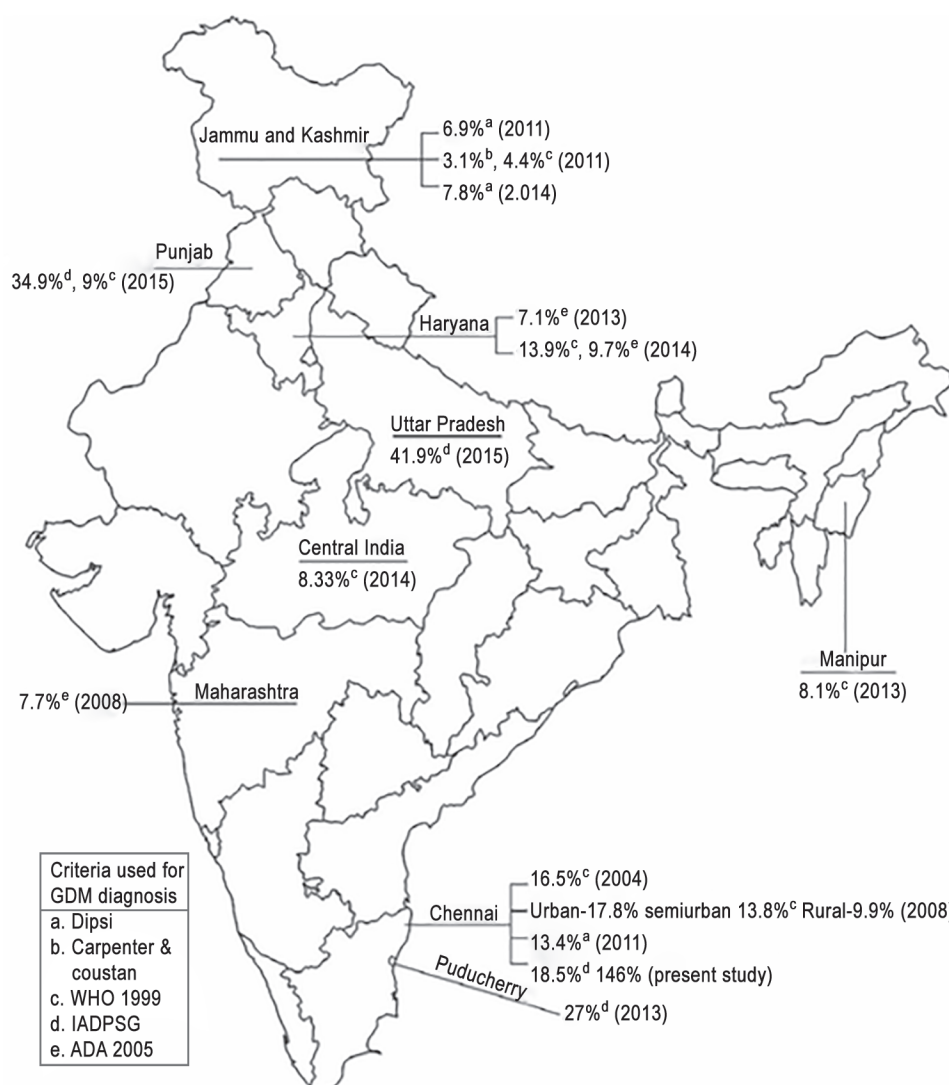


Fig. 1: Graphical representation of GDM prevalence across India

**Table 1:** Various studies and methods used in detection of GDM

Author name	City/state	Sample size	Prevalence (%)	Criteria used for GDM diagnosis
Seshiah et al <sup>4</sup>	Government Maternity Hospital, Chennai	3,674	16.5	WHO 1999
Seshiah et al	Chennai	4,151	Urban 17.8, semi-urban 13.8, rural 9.9	WHO 1999
Swami et al <sup>13</sup>	Maharashtra	1,225	7.7	ADA 2005
Seshiah et al	Chennai	1,463	13.4	DIPSI
Wahi et al	Government Medical College, Jammu	2,025	6.9	DIPSI
Nayak et al	Pondicherry Institute of Medical Science	304	27	IADPSG
Vanlalhrui et al	RIMS, Manipur	300	8.1	ADA 2005
Rajput et al	Post Graduate Institute of Medical Sciences, Haryana	607	7.1	ADA 2005
Zargar et al	Sher-i-Kashmir Institute of Medical Sciences	2,000	3.1 4.4	Carpenter and Coustan WHO 1999
Raja et al <sup>12</sup>	Government Medical College, Srinagar	306	7.8	DIPSI
Rajput et al	Rural Haryana	900	13.9 9.7	WHO 1999 ADA 2005
Kalyani et al	Central India	300	8.33	WHO 1999
Arora et al <sup>16</sup>	Ludhiana, Punjab	5,100	34.9 9	IADPSG WHO 1999
Gopalakrishnan et al <sup>17</sup>	SGPIMS, Lucknow	332	41.9	IADPSG

WHO: World Health Organization; ADA: American Diabetes Association; IADPSG: International Association of Diabetes in Pregnancy Study Groups; DIPSI: Diabetes in Pregnancy Study Group India

**Table 2:** Categorizing groups at risk for GDM<sup>20,21</sup>

Risk category	Clinical characteristics
High risk	<ul style="list-style-type: none"> <li>• Obesity</li> <li>• Diabetes in first-degree relative</li> <li>• Current glycosuria</li> <li>• Previous history of GDM or glucose intolerance</li> <li>• Previous poor obstetric outcome (unexplained intrauterine fetal death)</li> <li>• Previous history of macrosomia fetus or unexplained polyhydramnios</li> </ul>
Low risk	<ul style="list-style-type: none"> <li>• Age &lt;25 years</li> <li>• Belongs to low-risk ethnic groups (ethnic groups other than Hispanic, African-American, South Asian, East Asian, Pacific Islander, or Australian)</li> <li>• No diabetes in first-degree relative but present in distant relatives</li> <li>• No history of abnormal glucose tolerance previously</li> <li>• Normal prepregnancy weight and pregnancy weight gain</li> <li>• Previous living birth with no complications</li> </ul>

is implemented, patients with no recognized risk factors for GDM also undergo a 1-hour glucose challenge test (GCT) at 24 to 28 weeks of pregnancy.<sup>22</sup>

Fasting plasma glucose and postprandial plasma glucose have been shown to have low sensitivity as screening tests for GDM, and therefore, they are not recommended for screening.<sup>23</sup> In general, there are two approaches to the evaluation of women for GDM: The one-step approach and the two-step approach. In the one-step

approach, a diagnostic OGTT is performed without prior glucose screening. This approach is cost-effective. In the two-step approach, initial screening involves the GCT, which measures glucose concentration 1 hour after a 50 gm oral glucose load. The diagnostic OGTT performed only in the subset of women found to have glucose concentration values exceeding the normal levels.

## DIAGNOSTIC CRITERIA

While performing GCT, when the threshold for GCT is >140 mg/dL, the sensitivity is 80%; when it is 130 mg/dL, the sensitivity increases to 90%.<sup>1</sup> Whichever approach is used, the diagnosis of GDM is established only after performing an OGTT.

There are two major diagnostic criteria for the 3-hour 100-gm OGTT used: Carpenter–Coustan criteria and the National Diabetes Data Group (NDDG) criteria. The NDDG criteria were found to be less sensitive in diagnosing GDM and in predicting incidence of perinatal morbidities.<sup>24</sup> Alternatively, the American Diabetes Association (ADA) criteria for GDM diagnosis rely on a 75-gm glucose load and consider fasting serum glucose concentration, 1-hour glucose concentration, and 2-hour glucose concentration.<sup>25</sup> Again, two or more abnormal values are required for diagnosis. Although all these major criteria require two or more abnormal values for diagnosis, studies have shown that a single abnormal value is significantly associated with increased risk of perinatal morbidities.<sup>26</sup>

**Table 3:** Diagnostic criteria for GDM with their respective glucose values

Diagnostic criteria	Fasting (mg/dL)	1-hour (mg/dL)	2-hours (mg/dL)	3-hours (mg/dL)
100-gm OGTT Carpenter–Coustan (two or more abnormal)	95	180	155	140
100-gm OGTT NDDG (two or more abnormal)	105	190	165	145 (8.1)
75-gm OGTT ADA (two or more abnormal)	95	180	155	–
75-gm OGTT WHO (one or more abnormal)	92–125	≥180	153–199	–

The World Health Organization (WHO) recommends using a 75-gm glucose tolerance test for screening and diagnosis. When the WHO criteria are used, approximately twice as many patients will be diagnosed with GDM compared with other criteria. However, there is no proven additional clinical benefit with the use of WHO criteria (Table 3).<sup>27</sup>

## TREATMENT

Evidence shows that screening and treating GDM leads to reduction of perinatal morbidity and improvement in the post-delivery outcomes.<sup>28</sup> Good glycemic control has been shown to reduce adverse outcomes in the babies as well as the pregnant women with GDM.<sup>29</sup>

### Target Glucose Values

Experts recommend that women with GDM should maintain the following capillary blood glucose values: Fasting blood sugar <95 mg/dL, 1-hour postprandial glucose <140 mg/dL, and 2-hour postprandial glucose <120 mg/dL.<sup>1</sup> Other recommendations suggest maintaining fasting glucose levels between 90 and 99 mg/dL, 1-hour postprandial glucose levels of <140 mg/dL, and 2-hour postprandial glucose levels ranging between 120 and 127 mg/dL.<sup>30</sup>

Even if the recommended levels of glycemic control cannot be achieved, any improvement can be beneficial in reducing the perinatal complications, owing to the increased glucose levels.<sup>31</sup> Despite the benefits of glycemic control, studies on the contrary have shown that very low target glucose values (<87 mg/dL) are associated with increased rates of intrauterine fetal demise.<sup>32</sup>

### Medical Nutrition Therapy

The first line of management for women with GDM is dietary modification. Evidence indicates that MNT is effective in reducing pregnancy and perinatal complications and also in attaining glycemic control.<sup>33</sup> According to ADA recommendations, carbohydrate intake should be approximately 40% of total calorie intake and should be selected from foods with low glycemic index values.<sup>34</sup>

In pregnant women of normal body weight (BMI between 18.5 and 24.9), the recommendation is to consume 30 to 32 kcal/kg body weight. Those who are overweight

(BMI between 25 and 29.9) should ingest approximately 25 kcal/kg body weight and in obese women (BMI > 30), consumption should be 12 to 15 kcal/kg body weight.<sup>35</sup> 75 to 80% of women with GDM become euglycemic by following these caloric distribution guidelines. Caloric restriction should be approached cautiously, because studies show that elevated maternal ketone levels are associated with impaired psychomotor development.<sup>36</sup>

Compared with diet alone, exercise with dietary modifications has been found to lead to improved glycemic control.<sup>37</sup> The proposed mechanism for such an improvement in glycemic control is heightened sensitivity of peripheral tissues to insulin. A supervised home-based cycling program was helpful in maintaining normal postprandial glucose levels in pregnant women with diet-controlled GDM.<sup>38</sup>

Based on the available evidence on the benefits of exercise in managing GDM, ADA recommends moderate exercise programs for women without medical or obstetrical complications. For the general population, experts tend to recommend exercising three or more times a week for about 30 minutes.

### Pharmacotherapy

Pharmacological intervention in the management of GDM is usually employed when women fail to meet established goals with conventional therapy of diet and exercise. It is also indicated that elevated fasting glucose levels occur while on conventional therapy, because dietary modification has limited effect on these levels.

The pharmacological options mainly include insulin or oral hypoglycemic agents (Metformin and Glyburide).<sup>39,40</sup>

### Insulin

Insulin therapy is the most commonly used pharmacotherapy once MNT fails to achieve desired outcomes. Insulin regimens often include intermediate-acting insulins, such as isophane and short-acting agents, such as regular recombinant insulin (Humulin R). Pharmacotherapy can also involve the insulin analogs Aspart and Lispro. Insulin therapy decreases the frequency of fetal macrosomia and the risk of perinatal morbidity.<sup>41</sup>



**Table 4:** Glucose level cut-off points requiring insulin initiation in GDM

Guidelines	Fasting (mg/dL)	1-hour postprandial (mg/dL)	2-hour postprandial (mg/dL)
ACOG	>95	>130–140	>120
ADA	>90–99	>140	>120–127

Studies have shown that insulin analogs (Lispro and Aspart) are more effective as they get minimally transferred across the placenta, in comparison to regular human insulin in achieving targeted glucose values and minimizing the risk for macrosomia.<sup>42</sup> Because the insulin analogs have shorter duration of action and more rapid onset of action than regular insulin, they are associated with improved postprandial glycemic control and less postprandial hypoglycemia.<sup>43</sup> There are limited data on the use of long-acting insulins in pregnancy. For women with GDM who require insulin, isophane is therefore, the intermediate-acting insulin of choice (Table 4).

### Oral Hypoglycemic Agents

Oral hypoglycemic agents used in the management of GDM should be both effective and safe for the woman and developing fetus. With the exception of glyburide and metformin, oral hypoglycemic drugs are generally not recommended due to concerns about potential teratogenicity or prolonged neonatal hypoglycemia from drug transport across the placenta.<sup>44</sup>

#### Glyburide

Glyburide, one of the two oral hypoglycemic drugs used for the management of GDM, acts primarily to enhance insulin secretion by the pancreas. Studies have shown that glyburide, unlike other sulfonylureas, does not cross the placenta.<sup>45</sup> Certain factors are associated with higher rates of success with glyburide therapy, including initiation after 30 weeks gestation or fasting blood glucose levels <110 mg/dL and 1-hour postprandial glucose levels <140 mg/dL.<sup>46</sup> Despite several studies supporting the efficacy and safety of glyburide for women with GDM, ACOG, and ADA guidelines do not recommend its use until larger randomized controlled trials are completed on the subject.<sup>47</sup>

#### Metformin

Metformin is another oral hypoglycemic agent considered a potential substitute for insulin in GDM management. In a randomized controlled trial involving women with GDM, the use of metformin, whether alone or with supplemental insulin, was not associated with increased perinatal complications compared with insulin alone.<sup>48</sup> A meta-analysis done in 2013 revealed that metformin

is comparable to insulin regarding glycemic control and neonatal outcomes.<sup>49</sup> In another recent study, metformin use was associated with similar desirable outcomes when compared with MNT and insulin use.<sup>50</sup>

### Glucose Monitoring

In patients requiring insulin, the ideal frequency for glucose monitoring has not been established. In common practice, the patient generally checks glucose levels four times a day: Once upon waking in the morning, before meals, before bed, and 1 or 2 hours postprandial, to ensure adequate glycemic control. Postprandial glucose levels are preferable to fasting glucose levels, because they are more strongly associated with macrosomia. Insulin dose adjustments based on postprandial glucose levels rather than preprandial levels were shown to be associated with improvement in glycemic control and reduction of both maternal and fetal adverse outcomes.<sup>51</sup>

For women with diet-controlled GDM, there are no clinical guidelines regarding the frequency of monitoring. The general practice involves checking glucose levels two times per day at least 2 days per week; when two values exceed the limits over the course of a week, pharmacotherapy is recommended. Urine glucose monitoring is not useful in these patients.

## INTRAPARTUM MANAGEMENT

During labor, women on pharmacological therapy require hourly evaluations of their glucose values, while those with diet-controlled GDM do not require active glucose management. Patients on insulin therapy should be monitored by intermittent glucose monitoring and insulin should be administered based on sliding scale.

### Delivery

There is no definitive data on the timing delivery for pregnant women with GDM. If the patient has normal or near normal glucose values, it is recommended that she should be delivered at term. The general recommendation is that pregnancies complicated by GDM should not extend beyond term. Elective cesarean section has not been associated with significant reduction of birth trauma and has not been found to be cost-effective.<sup>52</sup> Earlier delivery was associated with reduction in chances of developing macrosomia but not with reduction of other neonatal complications.<sup>53</sup>

## POSTPARTUM MANAGEMENT

After delivery, insulin resistance usually resolves quickly, as does the need for pharmacological management. However, approximately 50 to 60% of affected women

will develop type II DM later in life. They are also at an increased risk of recurrent GDM that presents earlier in future pregnancies. An OGTT should be performed 6 weeks postpartum, 1 year post-delivery, and every 3 years thereafter.

## CONCLUSION

Gestational diabetes mellitus is associated with both maternal and fetal complications. Screening and managing women at appropriate gestational age is important to minimize adverse outcomes. Glycemic control can safely be achieved with a combination of nutritional and pharmacological interventions. Metformin and glyburide have been shown to be as effective as insulin in the management of GDM. Effective communication between physician, patient, and primary care provider is essential, for better management and successful outcome in GDM mothers.

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