Gestational diabetes mellitus (GDM) is one of the most common medical complications of pregnancy. It is defined as glucose intolerance with onset or first recognition during pregnancy. The prevalence of GDM is increasing, driven by advancing maternal age, racial/ethnic shifts in childbearing, and obesity. The incidence of GDM varies between countries and over time due to the different diagnostic criteria employed.

**Diagnosis of GDM**

Diagnostic criteria for GDM have changed over the decades, and several definitions are currently used. Various reasons account for the variation in diagnostic criteria including advances in assay technology, evolving access to care, epidemiology, and local cultural practices.

In Singapore, the diagnostic criteria recommended by the World Health Organization (WHO) are employed. Women with risk factors for the development of GDM are screened using a 75g, two-hour oral glucose tolerance test (OGTT). These risk factors include having a body mass index (BMI) of >25 kg/m², first-degree relatives with diabetes, history of previous GDM or large babies >4 kg, and/or history of poor obstetric outcomes usually associated with diabetes. With the 75g OGTT, GDM is diagnosed if fasting plasma glucose is 7.0 mmol/L and/or two-hour post-load plasma glucose is 7.8 mmol/L.

In 2008, the results of the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study were published. HAPO was a multinational prospective observational study that aimed to clarify the risks of adverse
Most cases of GDM probably represent chronic beta-cell dysfunction that is only detected during pregnancy, when glucose tolerance is checked as part of routine care and often for the first time in a woman’s life.

Diabetes and Pregnancy Study Groups (IADSPG) recommended using revised diagnostic thresholds for universal GDM screening. The new diagnostic cut-points for the fasting, one-hour and two-hour plasma glucose measurements were developed based on the glucose levels that conveyed an odds ratio for adverse outcomes of at least 1.75 compared with the mean glucose levels in the HAPO study. Based on the IADPSG recommendations, GDM is diagnosed via a 75g OGTT if fasting plasma glucose is 5.1 mmol/L, one-hour post-load plasma glucose is 10.0 mmol/L, and/or two-hour post-load plasma glucose is 8.5 mmol/L.

<table>
<thead>
<tr>
<th>Timing of glucose sampling during 75g OGTT</th>
<th>Glucose threshold (current WHO criteria) [mmol/L]</th>
<th>Glucose threshold (proposed IADPSG criteria) [mmol/L]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 min</td>
<td>7.0</td>
<td>5.1</td>
</tr>
<tr>
<td>60 min</td>
<td>-</td>
<td>10.0</td>
</tr>
<tr>
<td>120 min</td>
<td>7.8</td>
<td>8.5</td>
</tr>
</tbody>
</table>

*In both criteria, GDM is diagnosed when plasma glucose is at or above the threshold for any of the timed samples.

Although some countries and organisations have adopted the revised diagnostic criteria, the benefits of using the revised diagnostic criteria are uncertain at this time. Concerns about increased burden on healthcare resources have arisen as most of the available retrospective analyses show an increased prevalence of GDM if the new criteria are applied.

**Pathophysiology of GDM**

GDM is a generally mild form of hyperglycaemia that reflects inadequate pancreatic beta cell compensation for the body’s insulin needs. In some cases, the acquired insulin resistance of pregnancy (especially during the second half of pregnancy) can create insulin demands that exceed the capacity of beta-cells to supply insulin for the limited time frame of pregnancy alone.

However, most cases of GDM probably represent chronic beta-cell dysfunction that is only detected during pregnancy, when glucose tolerance is checked as part of routine care and often for the first time in a woman’s life. Studies have demonstrated that a large majority of the insulin secretory defect which is present in the third trimester of pregnancy is present before and soon after pregnancy. Insulin secretion during pregnancy in fact increases in parallel in women with and without GDM, but from a lower starting point in women with GDM. Moreover, clinical characteristics of the women in these studies suggest that they fall into the subtype of GDM that is related to Type 2 diabetes mellitus (T2DM). Therefore, many women with GDM seem to have a beta cell defect that is chronic rather than acquired during pregnancy.

Two subgroups of patients with GDM deserve mention. Firstly, some women have circulating immune markers (for example, antibodies to glutamate decarboxylase 65 or anti-islet cell antibodies) which are diagnostic of evolving Type 1 diabetes mellitus (T1DM). These autoantibodies are generally present in <10% of all women with GDM, and the frequency tends to parallel the background prevalence of T1DM in the population. Secondly, some women have genetic variants that are...
diagnostic of monogenic forms of diabetes. These women could have subtypes of maturity-onset diabetes of the young (MODY) and maternally inherited diabetes.\textsuperscript{14-16} These monogenic forms of diabetes in GDM appear to be rare, accounting for 1% to 5% of cases.

**Maternal and Foetal/Neonatal Risks of GDM**

Glucose crosses the placenta freely from the mother to the foetus. Untreated maternal hyperglycaemia exposes the foetus to higher than normal glucose concentrations and stimulates insulin production from the foetus’ pancreas. Excess fetal insulin secretion can lead to macrosomia, either from excessive fat deposition or as a direct growth effect of insulin. Mean maternal plasma glucose concentrations\textsuperscript{17} and foetal blood insulin levels\textsuperscript{18} are strongly correlated with neonatal birth weight. Maternal glycaemia during the third trimester is an independent predictor of birth weight in pregnancies complicated by GDM.\textsuperscript{19} Macrosomia, in turn, increases the risk of birth trauma and caesarean delivery. Women with GDM have an increased incidence of hypertensive disorders during pregnancy, including gestational hypertension, pre-eclampsia, and eclampsia.\textsuperscript{20-21}

GDM can also result in long-term health risks to both the mother and baby [see Table 2]. The link between GDM and postpartum diabetes in the mother has long been recognised. Majority of the cases of GDM are attributable to the metabolic stresses of pregnancy together with impaired insulin secretory response. The decreased beta-cell reserve in women with GDM can manifest in the decade after delivery. Even among women who have a normal postpartum OGTT, the risk of future diabetes may be up to seven-fold higher than in women without history of GDM.\textsuperscript{22} Currently, there is no evidence that treating GDM decreases the risk of developing diabetes later in life.

**Table 2. Maternal and fetal/neonatal risks of GDM**

<table>
<thead>
<tr>
<th>Maternal</th>
<th>Fetal</th>
<th>Neonatal</th>
<th>Child/Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth trauma</td>
<td>Macrosomia/ large for gestational age (LGA)</td>
<td>Hypoglycaemia</td>
<td>Obesity</td>
</tr>
<tr>
<td>Increased caesarean delivery</td>
<td>Birth trauma</td>
<td>Respiratory distress syndrome</td>
<td>Type 2 diabetes</td>
</tr>
<tr>
<td>Gestational hypertension, preeclampsia</td>
<td>Cardiomyopathy</td>
<td>Hyperbilirubinemia</td>
<td>Metabolic syndrome</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>Stillbirth</td>
<td>Hypocalcaemia, hypomagnesemia</td>
<td></td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td></td>
<td>Polycythemia</td>
<td></td>
</tr>
</tbody>
</table>

**Benefits of Treating GDM**

Two recent randomised controlled trials have demonstrated maternal and perinatal benefits from the treatment of GDM.

In the Australian Carbohydrate Intolerance Study (ACHOIS)\textsuperscript{21}, participants underwent a 75g OGTT between 16 and 30 weeks of gestation, and fasting plasma glucose of <7.8 mmol/L or two-hour post-load glucose of 7.8–11.0 mmol/L were used as the criteria for the diagnosis of GDM. Women with GDM were randomised to usual care (patients and providers blinded to the OGTT results) or intervention. In the intervention group, patients and providers were aware of the OGTT results. Treatment included individualised nutritional advice and self-monitoring of glucose. Exogenous insulin was given when glucose levels exceeded pre-specified targets. Treatment was associated with a significant reduction in the rate of the primary outcome, a composite of serious perinatal complications – perinatal mortality, shoulder dystocia, and birth trauma, including fracture or nerve palsy (adjusted relative risk 0.33; 95\% confidence interval 0.14–0.75). With treatment, the rates of LGA neonates and birth weight >4000g were reduced – from 22\% to 13\% and from 21\% to 10\%, respectively. Preeclampsia was also significantly decreased with treatment (12\% versus 18\%).

The Maternal-Foetal Units Network study\textsuperscript{23} employed a 100g OGTT, done between 24 and 30 weeks gestation, and GDM was diagnosed when at least two glucose values met or exceeded the following levels: fasting 5.3 mmol/L, 1-hour 10.0 mmol/L, 2-hour 8.6 mmol/L, 3-hour 7.8 mmol/L. Participants were randomised to usual care (blinded to the diagnosis) or intervention, similar to the ACHOIS study. A composite of clinically significant perinatal outcomes (mortality, trauma, jaundice, hypoglycaemia, or raised Cpeptide levels) occurred in the offspring at similar frequencies in the two groups. Treatment resulted in a lower frequency of LGA neonates and birth weight >4000g and decreased neonatal fat mass. Treatment also lowered the rates of caesarean delivery (26.9\% versus 33.8\%), shoulder dystocia (1.5\% versus 4.0\%), and gestational hypertension or preeclampsia (8.6\% versus 13.6\%).
Nonpharmacologic Treatment

Medical nutrition therapy remains the mainstay of GDM treatment. The optimal diet should provide caloric and nutrient needs to sustain pregnancy without causing significant postprandial hyperglycaemia. In general, a 1,900 to 2,400 kcal/day diet with carbohydrate restriction to 35% to 40% of calories is recommended. This should be calculated based on pre-pregnancy body weight and complex carbohydrates with high fibre should be encouraged.

Regular physical activity improves insulin sensitivity and can be a useful adjunct in GDM treatment. Several small studies have demonstrated the safety of exercise during pregnancy and the association with better cardiopulmonary fitness and mean glucose levels. At least 30 minutes of physical activity (such as walking after meals) several days a week are encouraged, although data is lacking on the effect of this level of exercise on pregnancy outcomes.

Pharmacologic Therapy

If nutritional therapy does not consistently maintain a fasting or preprandial glucose of <5.5 mmol/L and/or a one-hour postprandial glucose of <7.8 mmol/L or a two-hour postprandial capillary glucose of <6.7 mmol/L on two or more occasions within a one to two weeks interval, pharmacologic therapy should be considered.

Traditionally, exogenous insulin is the primary mode of pharmacologic treatment because of its safety in pregnancy, lack of significant transplacental passage, and history of use. Insulin therapy and regimen should be individualised to achieve glycaemic goals.

Although neutral protamine Hagedorn (NPH) insulin remains the basal insulin of choice in pregnancy, a recent randomised controlled trial has demonstrated the safety and efficacy of insulin detemir use in pregnancy. Two rapid-acting insulin analogues – insulin aspart and lispro – have been shown to be clinically efficacious with minimal transplacental transfer and no evidence of teratogenesis when used in pregnancy. Both insulin aspart and lispro may produce better postprandial control with less hypoglycaemia when compared to premeal regular insulin and should be considered if the woman develops frequent delayed postprandial hypoglycaemia while using regular insulin.

Two randomised trials have expanded the pharmacologic options for GDM. Langer et al compared glibenclamide (glyburide) with insulin in women who needed intensified treatment based on self-monitored glucose results. Equivalent perinatal outcomes were observed in the two groups. Only 4% of the women assigned to glibenclamide also received insulin to meet pre-specified glycaemic targets. The Metformin in Gestational Diabetes (MiG) study compared metformin with insulin in women with GDM. Perinatal outcomes were again similar in the two treatment groups. However, 46% of the women assigned to metformin in the study required supplemental insulin to achieve glycaemic targets. A preference for metformin over insulin was reported by the patients. Information in early childhood from the MiG study showed no adverse outcomes at the age of two years in the offspring of the two treatment groups. Thus, glibenclamide and metformin have been shown to be as effective as insulin for the treatment of GDM, although the effects on long-term health of the offspring are lacking at the present time. Metformin is currently approved by the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom for the treatment of GDM.

Management during Labour and Delivery

The timing and mode of delivery of women with GDM is controversial given the lack of data to support a particular recommendation. There is also no consensus on the timing of induction of labour in these women. Women with GDM should be monitored closely for excess foetal growth and induction is usually recommended when they exceed pre-specified parameters. During labour and delivery, the woman’s capillary blood glucose should be monitored every one to four hours and maintained at 4mmol/L to 7mmol/L to prevent neonatal hypoglycaemia. Women with GDM requiring pharmacologic therapy are best managed with intravenous dextrose and insulin infusions during labour.
similar to women with pre-gestational diabetes.

Postpartum Management

Majority of the women with GDM return to normal glucose tolerance immediately after delivery.1 Glucose-lowering treatment should be discontinued immediately after birth and the women should continue to have their blood glucose levels monitored.

The main emphasis of postpartum care for women with GDM is the assessment of future risk of diabetes mellitus and mitigation of that risk. A 75g, two-hour OGTT should be performed six to 12 weeks postpartum to detect persistent glucose intolerance.29,39 Lifestyle advice should be offered to women affected by GDM, aiming at diet modification, weight control, and increasing physical activity to reduce their risk of subsequent development of diabetes. The American Diabetes Association (ADA) currently recommends for lifelong screening for the development of prediabetes or diabetes at least once every three years in these women.39

As women with GDM are also at high risk for recurrence of GDM in future pregnancies, early evaluation of glucose intolerance should be carried out in future pregnancies.

Moving Forward

GDM will continue to remain one of the most common comorbidities of pregnancy, and its prevalence is expected to increase as obesity rates rise. More studies need to be conducted to elucidate the clinical and cost benefits of employing the proposed IADPSG diagnostic strategy and criteria. The role and safety of using oral glucose-lowering drugs in GDM will also need to be better defined with future research.

References


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