

**EDITORIAL****DIAGNOSIS OF GESTATIONAL DIABETES-ISSUES AND RECOMMENDATIONS**

Gestational diabetes mellitus (GDM) is defined as hyperglycemia with onset or first recognition in pregnancy. It is gradually becoming common in many population groups worldwide. Untreated GDM is associated with adverse outcomes both for mother and neonate including macrosomia and preeclampsia. These outcomes can be prevented if appropriate intrapartum treatment is instituted to maintain euglycemia. Hence the diagnosis and screening of GDM remains an area of special interest to both pathologists and treating clinicians. However over the years different diagnostic approaches have been put forward and still there remains considerable controversy about the optimal method of screening and diagnosis of GDM.

Normal pregnancy is associated with short-term variations in the body's control of glucose homeostasis. During first and early second trimester, blood glucose concentrations may be normal or low, but after around 20-28 weeks, insulin resistance is typical. Development of insulin resistance is likely to be multi-factorial in aetiology and may be caused by increasing concentrations of human placental lactogen, human placental hormone and tumor necrosis factor-alpha or falling concentrations of adiponectin. In all pregnant women, insulin requirements increase during this period and healthy pregnant women maintain euglycaemia by increasing its production.

Although, many women with GDM mount substantial insulin response, this compensatory increase is unable to effectively reduce fasting or postprandial glucose to euglycaemic concentrations. A number of different pathological processes could also contribute to gestational diabetes such as pre-existing insulin resistance, pre-existing insulin insufficiency and

pregnancy hormone-induced short-term disturbances in insulin release or function. These subtle pathological differences are poorly understood but may account for differences in maternal phenotypes, perinatal outcomes and long-term diabetes risk. Although diabetes during pregnancy which resolves in the postpartum period, was first described in the 19<sup>th</sup> century, the association of pregnancy diabetes with adverse outcomes was only determined around the middle of the 20<sup>th</sup> century.

O'Sullivan and Mahan were first to demonstrate that pregnant women had high postprandial glucose concentrations compared with non-pregnant women exposed to a 100g OGTT. They went on to study responses to a 100 g 3h OGTT and identified cutoff values for GDM based upon concentrations two standard deviations (SD) above the mean for each of the fasting, 1, 2, and 3 h post load glucose values. They suggested that two abnormalities should be required to make a diagnosis. This first set of diagnostic criteria aimed to identify women at risk of subsequent type 2 diabetes (T2DM) and affected women had a significant risk of developing T2DM in the following years.

The World Health Organization in 1999 recommended (modified WHO criteria) that the diagnosis of GDM should be based upon the 75 g OGTT. These recommendations are based upon the work of the International Association of the Diabetes in Pregnancy Study Group (IADPSG), who proposed diagnostic criteria which were based upon risks of negative pregnancy outcomes. These thresholds (75 g OGTT 0 h  $\geq$ 5.1; 1 h  $\geq$ 10.0; 2 h  $\geq$  8.5 mmol/L) were developed using data from the Hyperglycaemia and Adverse Pregnancy Outcomes (HAPO) study. However this criterion was based on a single

study, required a single abnormality to make the diagnosis and used lower fasting glucose thresholds than those recommended in previous WHO guidelines. This led to concerns about possible over diagnosis of GDM, increased health expenditure and the unnecessary medication of otherwise healthy pregnancies.

In the United Kingdom, The national institute for health and care excellence (NICE) have recently released updated guidelines on the diagnosis and management of patients with GDM. Based upon cost-effectiveness measures and standard costs of complications, NICE has recommended a new set of diagnostic criteria for GDM based upon a 75 g OGTT ( $\geq 5.6$  mmol/L fasting and  $\geq 7.8$  mmol/L 2 h value; no 1 h value). The 2015 NICE guidelines may increase the incidence of GDM in many populations when compared with the 2008 NICE guidelines.

The 2015 NICE thresholds have added to the controversy surrounding GDM diagnosis by failing to adopt criteria consistent with those of the WHO, which are based upon prospective evidence from the HAPO study. Although the threshold of 5.6 mmol/L is expected to improve outcomes compared with the previous threshold of 7.0 mmol/L, the NICE-2015 criterion has never been tested in clinical practice. It was derived from available research data on clinical outcomes and cost effective.

The issue of how best to identify women who have GDM is also complex and controversial. The WHO recommends universal screening of all pregnant women with the 75 g OGTT. However, this approach has important resource implications and considered unfeasible by many. NICE recommends (in both 2008 and 2015 guidelines) the use of a selective screening approach, where screening is only offered to women based upon risk factors including previous GDM, previous macrosomic infant, a

family history of diabetes in a first-degree relative, ethnic origin with a high diabetes prevalence or to women with obesity. Women with one or more risk factors should be offered a 75 g OGTT at 24–28 weeks' gestation. As risk factor based screening approaches are both practical and economical, they will tend to miss women who develop GDM in the absence of traditional risk factors.

Diabetes which is first diagnosed in pregnancy is often assumed to be GDM but can also be: (a) Pregestational undiagnosed or developing type 1 diabetes (T1DM), (b) Pre-existing undiagnosed T2DM, (c) MODY diabetes, (d) Pancreatic destruction for example, due to hypertriglyceridaemia. The patient's first visit to the antenatal clinic is the main opportunity to assess the underlying diagnosis.

GDM is generally managed with diet, exercise, metformin or insulin treatment and it usually resolves after delivery. Identifying and treating GDM improves maternal and fetal outcomes, and also reduces the risk of diabetes in later life. However, there remains considerable controversy about the optimal method of identification and diagnosis of women with GDM. The NICE-2015 criteria addresses cost-effectiveness issues, while the WHO-2013 guidelines are based upon identification of pregnancies at risk of peripartum complications. The Carpenter–Coustan criteria were devised to identify women at risk of diabetes in later life. These issues of cost-effectiveness and short- and long-term risks are all important, and an ideal set of diagnostic criteria would encompass all three aspects. Despite these discrepancies, it is imperative that older diagnostic thresholds are updated (fasting glucose  $>6-7$  mmol/L is too high) to reflect the recent changes in guidelines and evidence. A further issue relates to the performance of screening or diagnostic testing for GDM. Pregnancy offers unique challenges for

diagnostic testing as test performance also depends upon the gestational stage and red cell turnover. Current guidelines, both NICE and WHO have moved away from the GCT and towards the 75 g OGTT, performed in most women at 24–28 weeks' gestation. However, the possibility of early hyperglycaemia due to

undiagnosed overt diabetes, MODY diabetes or early onset GDM must always be considered/ruled out.

**Brig Tariq Mahmood Ahmad**

MBBS, MCPS, FCPS

Consultant Chemical Pathologist

Army Medical College/ National University of Medical  
Sciences (NUMS), Rawalpindi

Email: tariqmahmoodahmad81@gmail.com

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