

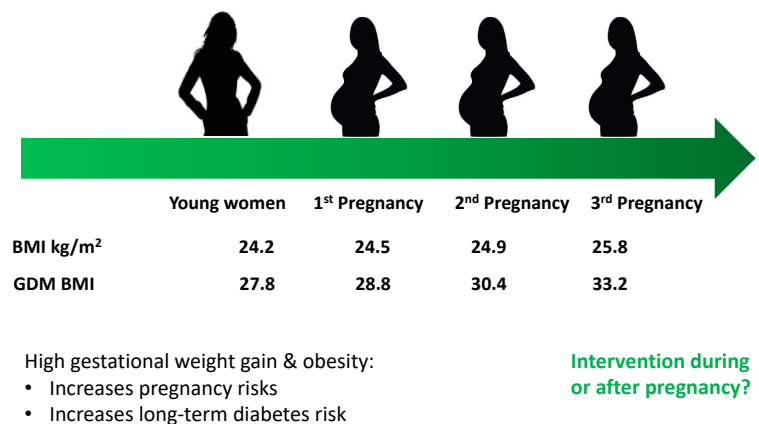
# Gestational Diabetes Mellitus: Latest Research and Guidelines

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One in six live births occur in women with diabetes, of which, by far the most common type, accounting for approximately 85% of all diabetes cases, is gestational diabetes mellitus (GDM).<sup>1</sup> GDM is a serious pregnancy-related condition, which increases the risk of pregnancy complications for both mother and child. It is of particular concern in low- and middle-income countries, which experience 85% of the annual global diabetes deliveries, and 90% of the most serious pregnancy complications. As women are increasingly entering pregnancy overweight and obese, the rates of GDM will likely rise further. Eight priority countries (India, Pakistan, Bangladesh, China, Indonesia, Nigeria, Brazil and Mexico) account for more than half of the global live births and global diabetes burden.

The maternal risks of GDM include pre-eclampsia, and increased obstetrical intervention including induction of labor and caesarean delivery. GDM often recurs in subsequent pregnancies, with recurrence rates of at least 40%-60% reported.<sup>2</sup> Women with a GDM pregnancy have a 70% increased risk of progression to type 2 diabetes (T2D) within 5-10 years. Women with higher pre-pregnancy body mass index (BMI) or higher gestational weight gain are most at risk. Every 1 kg increase in maternal pre-pregnancy weight is associated with a 40% increased risk of T2D. Women with excessive gestational weight gain also retain approximately 3 kg more up to 15 years after pregnancy. Data from our own clinic highlight the cumulative impact both of gestational and of inter-pregnancy weight gain across successive pregnancies (Fig 1).<sup>3</sup>

## THE ROAD TO OBESITY AND T2D



**Fig 1. Excessive gestational weight gain in women with GDM is associated with retained weight after pregnancy.<sup>3</sup>**  
GDM=gestational diabetes mellitus

Maternal hyperglycaemia stimulates fetal pancreatic insulin secretion leading to (1) increased fetal growth acceleration; (2) increased fetal fat accumulation; (3) large for gestational age (LGA), defined as birthweight >90th percentile; and (4) macrosomia, defined as birthweight >4000 g. LGA increases the risk of preterm and instrumental and/or operative delivery and stillbirth.<sup>4</sup> These delivery complications can lead to more permanent disabilities, including hypoxic brain damage, shoulder dystocia and Erb's palsy. Furthermore, LGA infants are themselves predisposed to developing insulin resistance, obesity and T2D perpetuating an intergenerational cycle of cardiometabolic disease.<sup>5</sup> Optimising maternal glucose control during pregnancy is therefore important both for a successful pregnancy outcome, and for longer-term health of both mother and child.

**GDM Screening** GDM screening can be either a one- or two-step process. In the two-step process, all women receive a 50 g one-hour glucose challenge test (GCT), and those who screen positive (typically defined as post GCT glucose of  $\geq 140$  mg/dL or 7.8 mmol/L) proceed to a formal 75 g oral glucose tolerance test (OGTT) diagnostic test. The GCT is a lower cost and less burdensome test, and can therefore be applied to all pregnant women. However, the benefits of a universal test have to be weighed against the potential delays (typically 10 days) before the formal diagnosis and initiation of treatment. The one-step approach involves a single 75 g OGTT, which is offered only to women who belong to a recognised high-risk group:

- Prior diagnosis of impaired glucose tolerance or previous GDM pregnancy
- Maternal age  $>30$  years
- Pre-pregnancy BMI  $>30$  kg/m<sup>2</sup>
- Multiple gestation
- Family history of diabetes (particularly in first-degree relative)
- Previous LGA infant or infant over 4.5 kg
- Ethnic origin with high prevalence of T2D (eg, Indian, Pakistani, Bangladeshi, Middle-Eastern, Caribbean)

The challenge with risk factor-based screening is that many women with GDM (in some populations up to 50%) have no recognised risk factors. In addition, risk factor screening is variably implemented with different cut-offs in maternal BMI applicable for different ethnic groups. Currently, the International Association of the Diabetes and Pregnancy Study Groups (IADPSG), World Health Organization (WHO), American Diabetes Association (ADA), UK National Institute for Health and Care Excellence (NICE), and Australasian Diabetes In Pregnancy Society (ADIPS) recommend the one-step screening approach. The UK NICE guidelines also advise that women with previous GDM have a 75 g 2-hour OGTT or self-monitoring of blood glucose in early pregnancy. The United States Preventive Services Task Force supports screening after 24 weeks, but not earlier.

**GDM Diagnosis** The recognition that the relationship between glycaemia and maternal-fetal outcomes is a continuum, as described in the Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) study, has created controversy regarding appropriate diagnostic thresholds.<sup>6</sup> Based on these findings, the IADPSG recommend that any of the following glucose cut-offs be considered diagnostic for GDM: (1) fasting  $\geq 5.1$  mmol/L; (2) 1-hour  $\geq 10.0$  mmol/L; or (3) 2-hour  $\geq 8.5$  mmol/L (92, 180 and 153 mg/dL respectively).<sup>7</sup> WHO and the ADA support the IADPSG diagnostic criteria. Different populations manifest different proportions of hyperglycaemia at each OGTT time point. For example, the proportion of women with GDM whose fasting glucose cut-off exceeds 5.1 mmol/L (92 mg/dL) is very context-specific and varies from 25%-75%. The UK (NICE) has recommended a higher fasting  $\geq 5.6$  mmol/L, but lower 2-hour cut-off  $\geq 7.8$  mmol/L (101 and 140 mg/dL, respectively). Data from our GDM clinic showed that the women missed by the higher fasting glucose proposed by NICE, were at higher risk than the additional women detected by the lower 2-hour cut-off.<sup>8</sup>

**GDM Treatment** Treatment of GDM is less controversial. An Australian trial confirmed that treatment of women with more severe hyperglycaemia reduced serious pregnancy complications, albeit with increased obstetrical intervention.<sup>9</sup> A subsequent trial also demonstrated improvements in obstetric and perinatal outcomes associated with treatment, mainly diet and lifestyle, in women with less severe hyperglycaemia.<sup>10</sup> All professional organisations therefore advise self-monitoring of blood glucose (SMBG) with diet and lifestyle modification as first line therapy. The recommended glucose control targets are typically (1) fasting glucose  $<5.3$  mmol/L (95 mg/dL); (2) 1-hour  $<7.8$  mmol/L (140 mg/dL); and (3) 2-hour  $<6.7$  mmol/L (120 mg/dL). This pragmatic clinical approach achieves satisfactory glucose control in approximately two thirds of women with GDM.

We have recently performed a systematic review and meta-analysis demonstrating that dietary interventions (in addition to routine clinical advice) can further optimise maternal glycaemia and reduce newborn adiposity.<sup>11</sup> However, the quality of the published trials do not support any particular diet (Mediterranean, low fat, low carbohydrate, low glycemic index, or total energy restriction) as being more or less effective. The take-home message is that any culturally acceptable dietary intervention is likely to be effective. Many professional organisations also recommend 30 minutes of moderate daily exercise throughout pregnancy. Up to one third of women require supplementary treatment to achieve their glycemic targets. The use of oral agents which cross the placenta (including both metformin and/or glyburide) remains controversial, leading the ADA and American College of Obstetricians and Gynecologists (ACOG) to recommend insulin as the preferred treatment option.

**Future Directions** Particular attention should be paid to the prevention of GDM in obese women who may already have accelerated fetal growth at an earlier gestational age. Randomised clinical trials of diet and lifestyle interventions and of metformin have failed to prevent development of GDM in obese women. As not all overweight and obese women develop GDM, more research is needed to develop better tools for the earlier detection (and treatment) of GDM in high-risk groups. More research is also needed regarding the most effective screening and diagnostic programmes for GDM in low- and middle-income countries. These may include biomarkers and/or direct assessment of maternal glucose using novel continuous glucose monitoring (CGM) systems. As CGM becomes an increasingly accessible and affordable treatment option for GDM, this may pave the way for improved risk assessment, personalised treatment, better management, and improved health outcomes for both mother and baby.

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