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Understanding the Significance of Hyperglycaemia in the First Trimester of Pregnancy

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Abstract

Gestational Diabetes Mellitus (GDM) has short and long-term implications for both maternal and fetal health. The incidence of GDM is increasing rapidly worldwide. Universal screening and treatment of GDM from 24 weeks gestation is well-established, however, uncertainty remains regarding the diagnostic accuracy as well as risks and benefits of treatment for women diagnosed with GDM earlier in pregnancy. Evidence is established for the diagnosis of GDM in women from 24 to 32 weeks gestation, based on the HAPO study which showed a robust linear association between increasing plasma glucose levels and a range of adverse pregnancy outcomes.

Keywords: Gestational diabetes mellitus; Early GDM; First trimester pregnancy; Hyperglycaemia in pregnancy

Description

Gestational Diabetes Mellitus (GDM) has short and long-term implications for both maternal and fetal health. The incidence of GDM is increasing rapidly worldwide [1]. Universal screening and treatment of GDM from 24 weeks gestation is well-established, however, uncertainty remains regarding the diagnostic accuracy as well as risks and benefits of treatment for women diagnosed with GDM earlier in pregnancy. Evidence is established for the diagnosis of GDM in women from 24 to 32 weeks gestation, based on the HAPO study which showed a robust linear association between increasing plasma glucose levels and a range of adverse pregnancy outcomes [2]. Additional treatment trials such as the Australian ACHOIS study and American Network study confirmed that intervention for GDM in women between 24 to 34 weeks gestation reduces serious perinatal and maternal fetal complications [3,4]. Following publication of the HAPO study data, the International Association of Diabetes and Pregnancy Study Groups consensus panel (IADPSG) revised the diagnostic criteria for GDM in 2010, recommending a Fasting Plasma Glucose level (FPG) of 5.1-6.9 mmol/L, 1-h plasma glucose level of ≥ 10.0 mmol/L and 2-h plasma glucose level of 8.5-11.0 mmol/L following a 2 hr 75 g Oral Glucose Tolerance Test (OGTT), and these thresholds are recognised by the World Health Organization (WHO) and the Australasian Diabetes in Pregnancy Society (ADIPS) [5-7].

International guidelines endorse screening for 'overt' diabetes early in pregnancy, to allow identification of high-risk women with undiagnosed pre-existing diabetes (FPG ≥ 7.0mmol/L, 2-h plasma glucose 11.1 mmol/L following a 2-h 75 g OGTT or a random plasma glucose 11.1 mmol/L in the presence of diabetes symptoms) to enable intensive intervention with the intention of improving pregnancy outcomes [5-7]. However, as an unintended consequence, screening also identifies a group of women with 'early GDM' who exceed the established IADPSG/WHO diagnostic criteria for later pregnancy. This 'early GDM' has been found to have a prevalence of up to 24% in an obese European population, with most women (79%) diagnosed based on a FPG ≥ 5.1mmol/L before 20 weeks gestation [8]. These women may be labeled as 'early GDM' and treated, despite ongoing uncertainty regarding the optimal diagnostic criteria for GDM in early pregnancy; a lack of clear evidence for intervention; and a potential risk of overtreatment with consequent medicalization of their pregnancy [9]. In fact, the IADPSG council has previously advised against the use of the current FPG threshold of ≥ 5.1 mmol/L prior to 20 weeks gestation [10].

The current literature investigating early pregnancy hyperglycaemia is sparse. One randomized-controlled trial of 922 women, performed in an at-risk population with BMI ≥ 30 kg/m2, failed to demonstrate a benefit of early screening at 14-20 weeks when compared to routine screening at 24-28 weeks; importantly there was no significant difference in a composite perinatal outcome of macrosomia, primary caesarean delivery, hypertensive disease of pregnancy, shoulder dystocia, neonatal hyperbilirubinaemia and neonatal hypoglycaemia [11]. A smaller, underpowered intervention trial of 157 women with hyperglycaemia (HbA1c 5.7-6.4% and/or FPG 5.1-6.9 mmol/L) prior to 16 weeks gestation, similarly did not show that early treatment, compared to treatment commenced from 28 weeks gestation, resulted in a significant improvement of maternal and neonatal outcomes [12].

Conversely, in favour of intensive management of 'early GDM', hyperglycaemia in early pregnancy has been linked with significant adverse maternal factors such as metabolic syndrome, obesity and insulin resistance [13]. These women may have poor pregnancy outcomes despite standard treatment and have an increased risk for a subsequent diagnosis of GDM later in pregnancy [14, 15]. A Chinese study demonstrated that 37% of women with FPG of 5.1 to 5.6 mmol/L in early pregnancy were diagnosed with GDM by 24 to 28 weeks gestation [16]. In contrast, a Spanish study showed that only 16% of women with first trimester FPG of 4.9-6.0 mmol/L subsequently developed GDM, but concerningly, a surprisingly stringent first trimester FPG threshold of ≥ 4.6 mmol/L was associated with an increased risk (OR 1.75) for large-for-gestational-age neonates [17]. Our recently published Australian cohort study of fifty consecutive women presenting to a tertiary care

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service with a FPG 5.1-5.6 mmol/L in the first trimester of pregnancy demonstrated that persistent hyperglycaemia, defined by IADPSG/WHO diagnostic criteria, occurred in 42% after 12 weeks gestation; double the rate of our background population GDM incidence of 17% [18]. A diagnosis of 'early GDM', concurrent obesity and advanced maternal age were all risk factors for a GDM diagnosis occurring in the second and third trimester of pregnancy. Unexpectedly, the neonates of women who were diagnosed with GDM later in pregnancy (86% of whom were treated medically with metformin and/or insulin) had a significantly lower birth weight compared to the neonates of women who did not receive a later diagnosis of GDM (3.3 kg versus 3.6 kg, $p<0.01$). All the women diagnosed with GDM birthed neonates weighing ≤ 4kg, but 17% of women with early hyperglycaemia but no subsequent GDM diagnosis delivered a neonate >4kg. These observed differences in neonatal birth weight may be explained by the preventative effect of active dietary support, effective metformin and insulin treatment in women diagnosed with GDM, and perhaps a trend towards an earlier birth for women with GDM (38.5 versus 39.5 weeks gestation at delivery; $p<0.001$) based on obstetric guidelines. Reassuringly, clinically relevant overtreatment of women with GDM appears unlikely as there was no evidence of growth restriction using birth centile data in these neonates. Alternatively, some women who remained below the glucose threshold following OGTT at 24-32 weeks gestation could have maintained maternal euglycemia as a consequence of the 'fetal steal phenomenon', in which the presence of fetal hyperinsulinaemia allows the fetoplacental unit to 'steal' maternal glucose, leading to accelerated neonatal growth despite the absence of a diagnosis of maternal diabetes [19].

Indeed, the optimal diagnostic FPG threshold in early pregnancy still requires an evidence-based definition. The relationship between glucose threshold and outcome may prove variable in different populations and at different timepoints up to 24 weeks gestation due to the expected physiological fall in FPG as pregnancy progresses [20]. Future randomised clinical trials, for example the TOBOGM study, should help establish if treatment of pregnant women with GDM diagnosed in early pregnancy can lead to an improvement in pregnancy, neonatal and maternal outcomes [21]. Based on the current available literature, our local data and a consideration of the potential for exposure during the COVID-19 pandemic, we propose a pragmatic approach with expectant management of women who have an incidental finding of FPG 5.1-5.5 mmol/L in the first trimester of pregnancy, followed by screening from 12 weeks gestation based on their risk profile (Figure 1).

	Early testing <12 weeks	**Early testing at 16-20 weeks**	**Usual testing at 24-28 weeks**	**Postnatal Testing**
Who to test	Consider for **high risk** women	For **high risk** women	For **all** women	For **all** women with GDM
Standard test	HbA1c and fasting glucose	75g OGTT (ADIPS criteria)	75 g OGTT (ADIPS criteria)	75g OGTT 6-12mths post-partum
ALTERNATIVE If gold standard not achievable	Used to exclude **overt diabetes** No alternative testing required as OGTT not recommended <12 weeks	Choose from: ➢ HbA1c and random glucose ➢ Fasting glucose ➢ 1 week of BGL monitoring	Choose from: ➢ HbA1c and random glucose ➢ Fasting glucose ➢ 1 week of BGL monitoring	Perform both: ➢ HbA1c and fasting glucose
Interpretation	Diagnose GDM if HbA1c ≥5.9% or fasting glucose ≥5.6mmol/l But if fasting glucose 5.1-5.5mmol/l repeat at 12+ weeks and diagnose GDM if fasting glucose ≥5.1mmol/l	Diagnose GDM if HbA1c ≥5.9% or random glucose ≥8.5mmol/l or fasting glucose ≥5.1mmol/l But if fasting glucose 4.7-5.0mmol/l progress to OGTT (ADIPS criteria)	Diagnose GDM if HbA1c ≥5.9% or random glucose ≥8.5mmol/l or fasting glucose ≥5.1mmol/l But if fasting glucose 4.7-5.0mmol/l progress to OGTT (ADIPS criteria)	Standard criteria
Next step	Retest at 16-20 weeks if this test normal	Retest at 24-28 weeks if this test normal	No further testing unless indicated	Screen at least every 2 years

Figure 1: A pragmatic approach to glucose testing for pregnant women during the COVID-19 pandemic.
Adapted from: Diagnostic testing for Gestational Diabetes Mellitus (GDM) during the COVID 19 pandemic: Antenatal and postnatal testing advice [provided by the Australasian Diabetes in Pregnancy Society (ADIPS), the Australian Diabetes Society (ADS), the Australian Diabetes Educators Association (ADEA), and Diabetes Australia (DA)].
High risk women: One of the following factors: BMI>35 kg/m^2, indigenous background, history of impaired glucose tolerance or GDM, polycystic ovary syndrome, previous unexplained stillbirth, previous baby with macrosomia, or cystic fibrosis, medication that may cause diabetes, e.g. steroids, antipsychotics, immunosuppressant or two of the following factors: Immediate family history of diabetes, age>35 years, BMI>30 kg/m^2, non-caucasian background, or poor obstetric history.

Conclusion

In conclusion, women with mild fasting hyperglycaemia in the first trimester of pregnancy may benefit from proactive management to prevent the risk of excess fetal growth, but it remains unknown whether providing treatment can lead to improved materno-fetal outcomes.

Our team manages mild hyperglycaemia in the first trimester pregnancy expectantly and intervenes for women who exceed diagnostic glycaemic criteria beyond 12 weeks gestation based on the current available literature. However, randomised controlled studies are needed to guide the optimal approach to clinical management.

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