

Diabetes and pregnancy

Pregnancy can be complicated by diabetes in two ways: women with existing diabetes (either type 1 or type 2) may become pregnant; alternatively, women can develop diabetes as a result of being pregnant (gestational diabetes mellitus [GDM]). The condition affects 2–5% of pregnant women. As with all forms of diabetes, the hallmark is glucose intolerance (evident as raised blood glucose concentration), so the strict definition of GDM is glucose intolerance with onset or recognition during pregnancy. For the vast majority of affected women, the glucose intolerance associated with GDM is mild and resolves soon after birth. Despite this, however, the condition has clinical significance because women with GDM are at increased risk of type 2 diabetes, or, much more rarely, type 1 diabetes later in life. The health of the developing baby is also threatened by GDM, but it is not clear how severe glucose intolerance has to be for it to affect fetal health adversely. For this reason the full significance of GDM and the criteria used to make the diagnosis have remained a subject for continued debate. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study, conceived well over a decade ago, was designed to assess the clinical significance of mild hyperglycaemia during pregnancy. Results of this major seven-year prospective study, involving almost 24,000 pregnant women around the world, were presented in June at a meeting of the American Diabetes Association. The HAPO study results will help to resolve several controversial issues surrounding GDM. Of particular significance to those working in clinical laboratories, the results will enable progress towards a more evidence-based, consensual approach to screening and laboratory diagnosis of GDM.

The maintenance of blood glucose concentration within normal limits depends on the action of two pancreatic hormones: insulin and glucagon. By its effects on the pathways of intermediary carbohydrate, fat and protein metabolism, insulin reduces blood glucose concentration. In contrast, the action of glucagon is to raise blood glucose (Fig 1). In health, the synergistic action of these two opposing hormonal effects helps to ensure that blood glucose concentration rarely rises above around 8.0 mmol/L nor falls below around 3.5 mmol/L. Levels are highest 30–60 minutes after food and are lowest in the morning after an overnight period without food (the fasting state).

Diabetes mellitus is a common chronic metabolic condition affecting close to 5% of the UK population, and is characterised by raised blood glucose (hyperglycaemia) due to absolute or relative deficiency of insulin. For around 10–15% of the diabetic population the problem is autoimmune damage to the β -cells of the islets of Langerhans in the pancreas, where insulin is synthesised. The absolute insulin deficiency that results from this pancreatic damage determines that patients suffering this kind of diabetes (type 1 diabetes) have a lifelong requirement for exogenous insulin, delivered by daily injection.

Type 2 diabetes, which accounts for almost all of the remaining 85–90% of the diabetic population, is characterised by

a combination of insulin resistance and impaired insulin secretion. Insulin resistance, which in essence is the reduced ability of tissue cells to respond to normal (physiological) amounts of insulin, is strongly associated with obesity, so that nearly all those with type 2 diabetes are, if not obese, at least overweight. This is in contrast to those suffering type 1 diabetes, who in general tend to be thin when first diagnosed.

Type 1 diabetes is usually diagnosed during childhood or the teenage years, whereas type 2 diabetes has until recently been a disease of adulthood. One of the public health concerns that arises from the increased prevalence of childhood obesity is that an increasing number of children are now being diagnosed with type 2 diabetes – once a very rare occurrence.

GLUCOSE TOLERANCE TEST

Hyperglycaemia is the hallmark of untreated diabetes, and a consistently normal blood glucose concentration is sufficient to exclude the diagnosis. Diabetes (either type 1 or type 2) is confirmed if a single fasting blood glucose is >6.1 mmol/L (plasma glucose 7.0 mmol/L) or random glucose (ie sample taken at any time) concentration is >10.0 mmol/L (plasma glucose 11.1 mmol/L) on at least two occasions. If there is strong clinical suspicion of diabetes and/or a family history of diabetes, but fasting and random blood glucose is raised

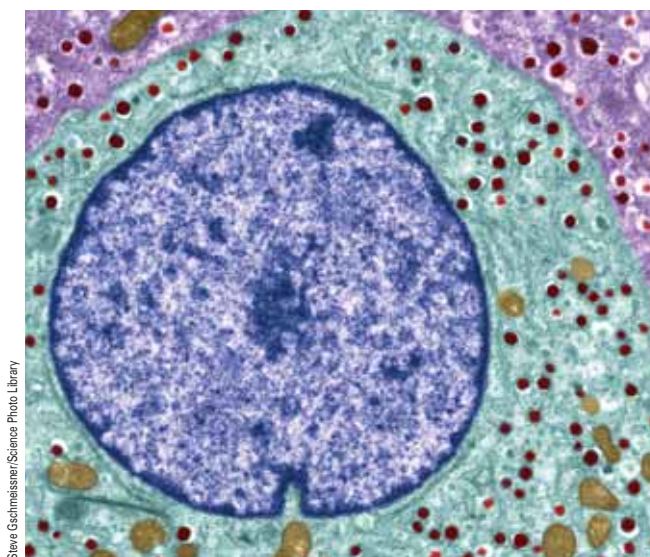


Fig 1. Coloured transmission electron micrograph of a glucagon-secreting α -cell, found in the islets of Langerhans of the pancreas. Glucagon balances the effect of insulin, which is produced by the β -cells of the pancreatic islets (original magnification $\times 10,000$).

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but not sufficiently high to make the diagnosis, an oral glucose tolerance test (OGTT) is indicated.

The OGTT permits examination of the effect that a standard glucose meal (load) has on blood glucose concentration. The test protocol is simple. After an overnight (at least 12 hours) period without food or drink (save water), blood is collected for fasting blood glucose estimation. A standard 75-g dose of glucose is then administered and blood is again sampled for glucose estimation exactly two hours later.

The normal response to ingestion of this glucose load is an initial increase in blood glucose concentration that stimulates insulin secretion. In turn, insulin reduces blood glucose concentration so that at two hours after glucose challenge blood glucose concentration is returning towards fasting blood glucose concentration. The patient with diabetes has insufficient insulin reserves and/or insulin effect to tolerate the standard (75 g) glucose load and blood glucose concentration remains abnormally high at two hours.

The precise criteria for diagnosis of diabetes following OGTT are described in Table 1. The terms impaired glucose tolerance and impaired fasting glycaemia are reserved for those patients whose glucose results are not sufficiently high to confirm a diagnosis of diabetes, but who are nevertheless abnormally high. Impaired glucose tolerance predates diabetes so that it is a risk factor for the future development of diabetes. Those who are found to have impaired glucose tolerance are therefore usually offered repeat OGTT at yearly or two-yearly intervals.

DIABETES TREATMENT

Diabetes is currently incurable. For those with type 1 diabetes, survival depends on a daily regime of insulin injections, and dietary adjustment is also necessary. For a minority of patients with type 2 diabetes, dietary adjustment may be all that is required, but most are also prescribed an oral hypoglycaemic (blood glucose lowering) agent. In the long term, some type 2 diabetics may require insulin injections.

The central aim of diabetic therapy is to maintain blood glucose concentration as close as is possible to that of the non-diabetic population. Normalisation of blood glucose not only eliminates the symptomatic acute

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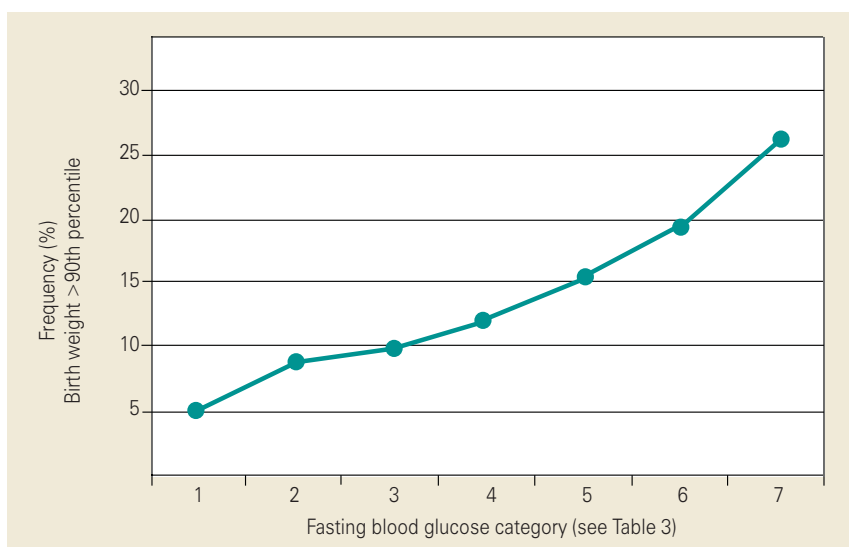


Fig 2. The effect of maternal blood glucose level on the frequency of high birth weight (macrosomia).

effects of diabetes that arise as a direct result of hyperglycaemia, but also reduces significantly the risk of the devastating long-term consequences of diabetes. These include coronary heart disease, renal disease leading to renal failure, eye disease that can progress to blindness, and painful peripheral nerve disease.

PREGNANCY AND PRE-EXISTING DIABETES

Normalisation of blood glucose is particularly important throughout pregnancy because hyperglycaemia can have serious adverse effects for fetal development as well as for perinatal and maternal health. For this reason, women with pre-existing diabetes are advised to plan pregnancies so that an assessment of health risk can be made prior to conception. During the weeks immediately following conception, the developing fetus of a woman with pre-existing diabetes whose blood glucose is not well controlled is at increased risk of congenital malformation and spontaneous abortion.

Babies born to diabetic mothers tend to be large for their gestational age, a condition called macrosomia. Evidence suggests that macrosomia is a consequence of maternal hyperglycaemia. Macrosomic babies can

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suffer birth trauma and may therefore need to be delivered by Caesarean section. They are at increased risk of hypoglycaemia, hypocalcaemia and jaundice during the immediate post-natal period. Pre-existing diabetes threatens maternal health during pregnancy in a number of ways, including increased risk of hypoglycaemia (particularly during early pregnancy), infection, polyhydramnios, hypertension and pre-eclampsia/eclampsia.

GESTATIONAL DIABETES

Normal pregnancy is a physiological state that is diabetogenic. From around half way through pregnancy, all women develop progressive insulin resistance that eventually becomes

Table 1. Interpretation of OGGT results in non-pregnant subjects.

	Fasting plasma glucose (mmol/L)	Plasma glucose two hours after 75 g glucose (mmol/L)
Normal	<5.5 (4.9)	<7.8 (6.7)
Impaired glucose tolerance	<7.0 (<6.1)	7.8–11.1 (6.7–10.0)
Impaired fasting glycaemia	6.1–7.0 (5.3–6.1)	
Diabetes mellitus	≥7.0 (6.1)	≥11.1 (10.0)

Figures in parentheses should be used for interpretation if blood glucose rather than plasma glucose is measured.

equivalent to that seen in those with type 2 diabetes. This pregnancy-associated insulin resistance is assumed to be due principally to the release of placental hormones (cortisol, human placental lactogen) that oppose the action of insulin. Insulin resistance is also increased by the increased adiposity that normally occurs as pregnancy progresses. In order to compensate for insulin resistance, pancreatic β -cells increase secretion of insulin.

Thus, normal pregnancy is characterised by insulin resistance and compensatory increase in insulin secretion. For the great majority of pregnant women the compensatory increase in insulin secretion is sufficient to maintain normal blood glucose regulation. For some, however, compensation is incomplete and the relative insulin deficiency leads to raised blood glucose concentration (glucose intolerance) and gestational diabetes during the final trimester.

An OGTT performed around 24–28 weeks is usually used to make a diagnosis of gestational diabetes, but there remains no consensus on the cut-off blood glucose values that should be used to make the diagnosis as there is for diabetes occurring outside of pregnancy. World Health Organization (WHO) recommendations are that gestational diabetes be diagnosed if fasting plasma glucose is >7.0 mmol/L or plasma glucose two hours after a 75-g glucose load is >7.8 mmol/L. Thus, cases of gestational diabetes diagnosed using these criteria include all those with impaired glucose tolerance (Table 1).

The WHO criteria are used in the UK and Europe, but GDM diagnosis in the USA is based on blood glucose concentration one hour after oral administration of 50-g glucose or alternatively on blood glucose concentration one hour, two hours and three hours after oral administration of 100-g glucose.

Controversy also surrounds screening policies that determine which pregnant women should be offered an OGTT. In some countries all pregnant women are offered a screening test (either random or fasting blood glucose), but that has been deemed inappropriate by UK authorities. Here, the decision to screen is decided in a rather *ad hoc* way after consideration of the risk factors (Table 2). In some centres, for example, screening would not be offered to those at low risk, but it might be offered to

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Table 2. Risks for gestational diabetes.

Factors indicating a low risk of gestational diabetes
• age <25 years
• low-risk ethnicity (ie other than Hispanic, Asian, native American, native Australian)
• no family history of diabetes
• no prior poor obstetric outcomes
Factors indicating a high risk of gestational diabetes
• obesity
• family history of diabetes
• prior delivery of a macrosomic infant
• history of glucose intolerance
• glucose detected in urine (current)

those at medium risk. Those in the high-risk category might be screened or perhaps proceed directly to glucose tolerance testing.

The controversy surrounding screening, diagnosis and management of gestational diabetes is due in large part to a gap in knowledge about the significance of mild hyperglycaemia. While it is clear from studies of women with diabetes prior to pregnancy that marked maternal hyperglycaemia is potentially harmful to the developing baby, it remains unclear whether or not the mild hyperglycaemia evident in the vast majority of women with gestational diabetes poses any threat beyond a long-term risk of type 1 or type 2 diabetes for the mother. This issue is addressed by the recently completed Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study.

THE HAPO STUDY

The hypothesis tested by the HAPO study is that 'hyperglycaemia in pregnancy less severe than overt diabetes mellitus is associated with increased risk of adverse maternal, fetal and neonatal outcomes that is independently related to the degree of metabolic disturbance'. During a seven-year study period, 23,325 pregnant women were

Table 3. Stratified distribution of fasting blood glucose concentration among 23,325 pregnant women (28 weeks' gestation).

Fasting blood glucose (mmol/L)	Number	% study population
<4.2	4060	17.4
4.2–4.4	7532	32.3
4.5–4.7	6199	26.6
4.8–4.9	2748	11.8
5.0–5.2	1893	8.1
5.3–5.5	674	2.9
>5.6	219	0.9
	23,325	100

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recruited at 15 centres in nine countries around the world, including two UK centres (Royal Victoria Hospital, Belfast, and St Mary's Hospital, Manchester).

At around 28 weeks' gestation (range 24–32 weeks) each pregnant study participant was submitted for an oral 75-g glucose tolerance test that included blood collection for fasting glucose and glucose at one hour and two hours post glucose ingestion. If glucose results exceeded a predefined threshold unequivocally consistent with a diagnosis of diabetes (ie fasting glucose >5.8 mmol/L or two-hour glucose >11.1 mmol/L) the pregnant woman in question was removed from the study (for ethical reasons) and treated.

For all the remaining women (the vast majority), test results were blinded to care staff and the pregnancy was monitored without intervention to the outcome. The study defined four main outcome measures: birth weight (presence of macrosomia), need for Caesarean section, presence of neonatal hypoglycaemia, and cord blood insulin concentration.

Maternal blood glucose concentration was found to be related independently to all four outcomes. Table 3 and Figure 2 provide an example of the way in which the data were presented, in this case examining the relationship between fasting blood glucose and birth weight. Table 3 describes the distribution of fasting blood glucose among the 23,325 pregnant women, stratified to seven levels. From Figure 2 it is clear that there is a linear relationship between maternal fasting blood glucose and the risk of delivering a macrosomic baby that holds even across the normal range (<4.2 – 5.2 mmol/L) for pregnant women. The same relationship held for one-hour and two-hour glucose values, and a very similar pattern of results was revealed when the other three main outcome measures were examined.

This important study has revealed that even mild hyperglycaemia poses an independent risk to neonatal health. The HAPO study hypothesis is proven and it now seems likely that the maternal blood glucose concentration at which a diagnosis of gestational diabetes is made will be lowered. Consequently, a higher proportion of pregnant women will receive a diagnosis of gestational diabetes and be treated to reduce blood glucose concentration. ■