Commentary

Diabetes mellitus is one of the most common and important medical complications affecting pregnancy. The number of pregnant women with diabetes is rising worldwide.

Diabetes can pre-date the pregnancy ('pre-existing diabetes') or arise during pregnancy ('gestational diabetes', GDM). Typically, GDM resolves once the pregnancy has ended. However, about 3% of women with a diagnosis of GDM actually have type 2 diabetes diagnosed for the first time in pregnancy and therefore it persists after the pregnancy is over. About 30% of women with GDM will develop type 2 diabetes within 10 years, and up to 50% over a longer period.

The coexistence of diabetes of any type and pregnancy is associated with an increased risk of adverse outcomes for both the woman and the baby, in particular macrosomia and resulting difficulties at delivery (such as shoulder dystocia). However, with appropriate management by a multidisciplinary team before, during and after delivery these risks can be minimised. Women with pre-existing diabetes should be counselled before pregnancy about the implications of pregnancy, and given particular support to optimise blood glucose control and the management of related medical complications when trying to conceive.

During pregnancy, women should be offered screening for GDM. This can be either 'universal' in which all pregnant women are screened, or only those with 'risk factors', such as a body mass index (BMI) >30, previous gestational diabetes or macrosomia, or a first-degree relative with diabetes. Screening for GDM is only for women not known to have a diagnosis of diabetes.

Women with either pre-existing diabetes or GDM require multidisciplinary care during the pregnancy. Assiduous blood glucose monitoring is essential to allow adjustment of medication with the aim of achieving blood glucose values within the normal range. Pregnancy is a diabetogenic state and in known pre-existing diabetes more insulin or oral hypoglycaemic medication will be needed. The closer maternal blood glucose values are to normal, the lower the likelihood of adverse outcomes in the woman and the baby. In addition, women are offered medications to lessen the likelihood of complications; for example, low-dose aspirin to reduce the risk of pre-eclampsia in the woman, and folic acid to reduce the risk of neural tube defects in the fetus. Apart from aiming for optimal blood glucose control, women should be monitored for the complications of the diabetes. Fetal assessment in the pregnancy includes accurate ultrasound measurements, especially in the first trimester to optimise dating of the pregnancy and throughout pregnancy, screening for fetal abnormality and ongoing surveillance of fetal growth, placenta function and amniotic fluid volume.

Every woman with diabetes in pregnancy should be offered a delivery plan discussion. This covers the timing and method of delivery, which are influenced by factors including the quality of blood glucose control and the presence of maternal and/or fetal complications. Irrespective of the method of delivery, caregivers should aim to maintain normal glucose values. In labour, a continuous glucose and insulin infusion will best maintain glucose homeostasis, and the fetal heart rate should be continuously monitored.

After delivery, blood glucose levels in women with pre-existing diabetes usually return to pre-pregnancy values, and most women with GDM will have normal blood glucose values with treatment. However, about 3% will need ongoing care of their diabetes, usually in the form of oral hypoglycaemic agents. All women with GDM should be offered annual screening for diabetes to identify the development of type 2 diabetes.

For at least the first 72 hours after the delivery, the baby should receive close surveillance for and treatment of possible complications, hypoglycaemia in particular.

Despite the progress made in the understanding, screening and management of gestational diabetes and pre-existing diabetes in pregnancy, controversies remain, which is evident in differing professional society guidelines. For example, although there is agreement that treatment of GDM has benefits, there is a still a lack of a clear threshold for increased risk of adverse pregnancy outcomes, which was made very clear by the Hyperglycaemia and Adverse Pregnancy Outcomes (HAPO) study, which demonstrated that the association between maternal plasma glucose concentrations (for both fasting and post-glucose challenge values) and adverse pregnancy outcomes is linear and continuous, with no inflection point.

Furthermore, there is no good evidence to support treatment of GDM at International Association of Diabetes and Pregnancy Study Group (IADPSG) thresholds. The inevitable additional diagnoses of GDM based on IADPSG thresholds increases the burden of diagnosis to both patients and the healthcare system. Finally, although it is recommended that women with GDM get tested for type 2 diabetes six weeks postnatally, the reality is that many women do not attend this testing and alternative approaches are needed. Not surprisingly, this current situation has left healthcare providers without consensus guidelines, resulting in the variability in care for GDM.

Another inherent problem is the definition of GDM, " . . . any degree of glucose intolerance of onset or first detected in pregnancy irrespective of whether the condition persists after pregnancy (and) does not exclude the possibility that (it) antedated pregnancy". This definition conflates trivial increases in maternal glucose with overt but previously unrecognised diabetes

(usually type 2) and wrongly implies that the risks are the same across this spectrum. The woman with unrecognised diabetes has significant adverse outcomes (congenital anomalies and stillbirth) compared to the true GDM patient. In communities with a high local prevalence of type 2 diabetes and obesity having the condition being detected first during pregnancy is not uncommon, and screening strategies for early pregnancy detection are needed.

More research is therefore needed to progress from the current broad agreement that pregnant women should be screened for GDM towards reaching consensus on optimal screening, diagnostic criteria, treatment, or post-delivery screening.

1 Introduction

Diabetes mellitus is one of the most common and important medical complications affecting pregnancy [1,2]. The rising prevalence and burden of diabetes worldwide has led to an increasing number of women being affected by pre-existing diabetes mellitus in pregnancy and gestational diabetes mellitus (GDM) [3,4].

2 Epidemiology

The prevalence of diabetes mellitus worldwide has been steadily increasing in recent years, in part due to the rising average body mass index (BMI) [5,6]. In addition, women have also been deferring childbirth till later in life, which has led to an increased incidence of cases of both pre-existing diabetes in pregnancy and GDM. There are also changing thresholds to defining GDM and differing screening practices exist. It is estimated that diabetes mellitus affects about 1 in 6 (17%) pregnancies. Of these, about 14% had pre-gestational diabetes and 86.4% have GDM [7].

3 Pathophysiology

The fetoplacental unit requires glucose as the main energy substrate. As fetal gluconeogenesis is minimal, the fetus is dependent on placental glucose transfer via glucose transporter proteins (GLUTs). Maternal insulin sensitivity varies over the course of the pregnancy (see Figure 1) [8]. Peak insulin sensitivity occurs between 9 and 16 weeks' gestation, which predisposes insulin-treated women to hypoglycaemia. Thereafter, insulin resistance and insulin requirements continue to rise, with a peak and then plateau at around 36 weeks' gestation. Insulin resistance increases in pregnancy due to placental hormones, including human placental lactogen, progesterone, prolactin, placental growth hormone and cortisol. Increasing insulin resistance is associated with compensatory hyperinsulinaemia in non-diabetic pregnancy. In women with pre-existing diabetes mellitus, the compensatory rise in endogenous

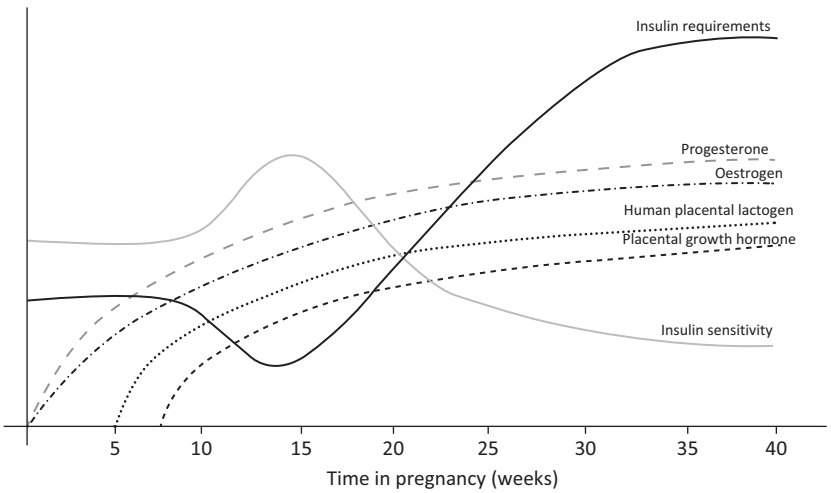

Figure 1 Insulin requirements and sensitivity throughout pregnancy [8].

insulin production does not occur, with resultant greater maternal hyperglycaemia, especially postprandial.

In addition, pregnancy is a state of 'accelerated starvation', where there is an exaggerated response to overnight fasting compared to the non-pregnant state. This means there is a greater fall in plasma glucose and amino acids, and a more pronounced rise in free fatty acids with enhanced ketogenesis during periods of fasting during pregnancy [9].

4 Classification of Diabetes in Pregnancy

Pregnancy can be affected by either pre-existing diabetes (DM) or gestational diabetes mellitus (GDM), which is diagnosed in pregnancy.

Pre-existing Diabetes Mellitus

Pre-existing diabetes mellitus is defined as women who have either type 1 or type 2 diabetes and less commonly maturity-onset diabetes of the young (MODY) before pregnancy. Glucokinase (GCK) MODY (MODY 2) or hepatocyte nuclear factor 1a (HNF1a) MODY (MODY 3) are the two most common types of MODY. Glucokinase MODY is an interesting condition, as the pregnancy outcome is dependent on the fetal carrier status for GCK mutation (50%), where fetuses without the GCK mutation are at higher risk of macrosomia. As such, regular fetal growth assessment can help establish appropriate glucose targets for women with known or suspected GCK

mutations. Other less-common causes of DM include pancreatitis and iatrogenic diabetes secondary to medications such as glucocorticoids and antiretroviral therapy.

Gestational Diabetes Mellitus

Gestational diabetes mellitus has been defined as any degree of glucose intolerance with onset or first recognition during pregnancy. It may reflect previously undiagnosed pre-existing diabetes. Women with GDM have at least a sevenfold increased risk of developing DM in the future [10]. Because of the increasing worldwide prevalence of undiagnosed type 2 diabetes mellitus in non-pregnant women of childbearing age, several screening algorithms, based on expert consensus, have been advocated to identify women with pre-existing diabetes which is first detected during pregnancy to differentiate them from true gestational diabetics [11,12,13]. This has clinical implications, because the risk profiles for the two groups are different. Women with pre-existing diabetes are more likely to develop microvascular complications such as retinopathy and nephropathy [14,15,16] and are at increased risk of congenital malformations associated with pre- compared with gestational diabetes [17,18].

5 Maternal, Fetal and Neonatal Risks of Diabetes in Pregnancy

Diabetes in pregnancy is associated with increased risks of adverse maternal, fetal and neonatal outcomes during pregnancy (Table 1) [8]. These correlate largely with maternal glycaemic control [19,20]. Whereas many of the risks of diabetes in pregnancy are common across all types of diabetes, women with type 1 and type 2 diabetes mellitus face additional risks, such as increased risk of congenital malformations, stillbirth, severe hypoglycaemia, diabetic ketoacidosis and worsening of existing microvascular disease [21,22]. Screening for GDM in pregnancy is important because of the higher risk of complications in pregnancy as well as long-term cardiometabolic complications [2,22].

The rates of pregnancy loss from miscarriage for both type 1 and type 2 DM are similar, but the risk factors differ, with losses in type 1 DM most commonly being attributable to major congenital anomaly and prematurity, whereas for type 2 it is stillbirth and chorioamnionitis [23,24]. Pregnant women with pre-existing diabetes are more likely to develop microvascular complications such as nephropathy and retinopathy, which can worsen during pregnancy [15]. The incidences of diabetic nephropathy in women with type 1 and type 2 diabetes are reported as 5–10% and 2–3%, respectively [15,16]. Diabetic retinopathy affects almost 50% of women with type 1 and 14% with 2 diabetes [25].

Table 1 Adverse pregnancy outcomes associated with diabetes in pregnancy [8]

Maternal	Fetal	Neonatal
• Hypoglycaemia • Diabetic ketoacidosis • Pregnancy-induced hypertension and pre-eclampsia • Diabetes-related complications (retinopathy, nephropathy)# • Perineal lacerations • Operative vaginal delivery • Caesarean section • Postpartum haemorrhage • Infection • Risk of DM with history of GDM*	• Miscarriage • Intrauterine death • Stillbirth • Congenital malformations# • Intrauterine growth restriction • Fetal macrosomia	• Preterm delivery • Shoulder dystocia • Birth injuries • Hypoglycaemia • Polycythaemia • Hyperbilirubinaemia • Hypocalcaemia • Respiratory distress syndrome • Obesity and metabolic syndrome in the future

*Risks unique to GDM; #risks unique to pre-existing DM.

6 Management Options for Diabetes in Pregnancy

Pre-pregnancy (Women with Pre-existing Diabetes)

General

Preconception care should be part of the routine care for all women of reproductive age with pre-existing diabetes. It should be provided by a multidisciplinary team comprising an obstetrician, endocrinologist, specialised diabetes nurse and dietician who should provide women with knowledge and advice to optimise their health for the best outcomes when they become pregnant.

A recent UK National pregnancy in Diabetes Audit report 2020 [26] recommends:

- Having dedicated pre-pregnancy coordinators focusing on pre-conception preparations, such as enhancing provision of contraception and folic acid administration, and the improvement of glycaemic control, especially in women with pre-existing diabetes living in deprived regions. Pregnancy preparation rates are lowest in women from the most deprived communities – only