Diabetes in pregnancy

Rebecca S Black, Michael DG Gillmer

Diabetes is the most common medical disorder of pregnancy and the incidence of type 2 diabetes is increasing. Although pregnancy outcomes have improved for both mother and baby over past decades, much needs to be done to reach the aspiration of similar outcomes to nondiabetic pregnancies, which many believe to be a realistic goal. Improvements can be achieved through better multidisciplinary management, although the best approach to gestational diabetes remains controversial.

Introduction

The first case report of gestational diabetes mellitus appeared in 1824, with a description of a mother with thirst, polyuria and glycosuria and the death of a macrosomic infant from shoulder impaction. Before the introduction of insulin in 1921, few women with type 1 diabetes became pregnant; those who survived childhood were generally underweight, amenorrhoeic and infertile. In those who did conceive, the maternal mortality rate was approximately 40% (mainly because of ketoacidosis) and fetal and neonatal survival was less than 50%.

Insulin has led to a dramatic improvement in maternal survival. However, compared with nondiabetic pregnancies, perinatal mortality remains five times higher and the incidence of congenital malformations up to ten times higher. This fails to meet the goal of the St Vincent Declaration, which states that the outcome of diabetic pregnancy should approximate that of the nondiabetic pregnancy.

Diabetes complicates approximately four per 1000 pregnancies, making it the most common pre-existing medical disorder in pregnancy. Type 2 diabetes is increasing in frequency.

Prepregnancy consultation

Ideally, women should be seen preconceptually. Tight glycaemic control is statistically associated with a reduced incidence of congenital malformations. There is also an opportunity to address obesity at this time, as many type 2 diabetics are overweight and obesity constitutes a major risk factor in pregnancy.

The need for special prepregnancy diabetic clinics has been questioned because they tend not to attract those with poor control who are at most risk and many pregnancies are unplanned. Therefore, the roles of the GP, diabetologist and diabetes nurse specialist are crucial. However, many women may not be aware that they have type 2 diabetes, clearly making preconceptual care impossible.

Treatment is aimed at achieving normoglycaemia. Maternal glucose values should ideally remain at 4–6 mmol/l. Normoglycaemia is associated with normal levels of other nutrients, such as amino acids and lipids. A diet high in complex carbohydrates is recommended; fat worsens insulin resistance and the total number of calories is also important. Many women will need to increase the frequency of both insulin injections and blood glucose monitoring to improve their control. Most women will achieve optimal control using a regimen of thrice-daily short acting insulin before meals together with an intermediate acting preparation at night. Continuous subcutaneous insulin via a pump may enhance control in some women.

Other general advice, for example about smoking and alcohol, should not be forgotten. Folic acid should be taken periconceptually (5 mg/day).

Those women with type 2 diabetes treated with oral hypoglycaemic agents are usually converted to insulin. However, there is growing evidence for the use of metformin in pregnancy, especially as it is now being used for the treatment of women with polycystic ovary syndrome, in whom it may decrease the rate of first-trimester miscarriage. There has also been some interest in the use of oral hypoglycaemic medications later in pregnancy for gestational diabetes.

Booking visit

Women should attend a specialist diabetic clinic as soon as their pregnancy is confirmed. This

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A record must be made of prepregnancy insulin requirements, as this information has often been forgotten in the postpartum period when it is required. Nausea and vomiting can make management of blood glucose concentrations difficult and women often need support and frequent antenatal visits throughout the first trimester. Women with persistent vomiting must be admitted to hospital.

Hypoglycaemia can be a serious problem and affects up to 70% of women. It is not detrimental to the fetus but pregnant women are often less aware of its presence. There were four cases attributed to diabetes in the last Report on Confidential Enquiries into Maternal Deaths (1997–99). Of these, three were attributed to hypoglycaemia. For this reason, all partners of pregnant women with diabetes should be given a glucagon kit and taught how to use it.

Proteinuria detected on routine testing warrants a 24-hour urine collection and tests of renal function.

An ultrasound scan to assess fetal viability is advisable, as there is an increased risk of miscarriage. Crown–rump length should be measured to assist in achieving accurate gestational dating, although in some diabetic pregnancies there may be early growth delay, which is associated with an increased incidence of congenital malformations.

Although the incidence of chromosomal abnormalities is not increased in diabetic pregnancies, antenatal screening should be offered. If the triple test is used a different reference range is required, because alpha-fetoprotein, unconjugated oestriol and human chorionic gonadotrophin levels are all lower in pregnant women with diabetes compared with pregnant women without diabetes. Nuchal translucency scanning can also be performed but has not been validated independently in diabetic pregnancy. The risk of other congenital abnormalities is increased (Table 1). For this reason, all women should be offered an anomaly scan at around 20 weeks of gestation as well as more detailed cardiac scans at 20 and 32 weeks of gestation.

Fundoscopy should also be performed in pregnant women with diabetes. Those with longer duration diabetes and more advanced forms of retinopathy are at greatest risk of disease progression during pregnancy; these women should be referred to an ophthalmologist.

All women with diabetic nephropathy should have a 24-hour urine collection for baseline measurements of proteinuria and creatinine clearance (ideally prepregnancy). Risks of nephropathy include renal failure, superimposed pre-eclampsia, fetal-growth restriction, stillbirth and preterm delivery.

### Diabetic emergencies

Diabetic ketoacidosis is rare but serious in pregnancy. It is usually preceded by a gradual onset of polyuria and drowsiness. Presenting symptoms and signs include dehydration, tachypnoea, hypotension, deep sighing respirations and ketotic smell. Treatment is based on...

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**Table 1. Congenital anomalies seen in infants of diabetic mothers**

<table>
<thead>
<tr>
<th>System</th>
<th>Abnormality</th>
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<tbody>
<tr>
<td>Central nervous system</td>
<td>Anencephaly</td>
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<td></td>
<td>Encephalocele</td>
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<td></td>
<td>Meningomyelocele</td>
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<td></td>
<td>Spina bifida</td>
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<td></td>
<td>Holoprosencephaly</td>
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<tr>
<td>Cardiac</td>
<td>Transposition of great vessels</td>
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<td></td>
<td>Ventricular septal defect</td>
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<td></td>
<td>Sinus inversus</td>
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<td></td>
<td>Single ventricle</td>
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<td></td>
<td>Hypoplastic left heart</td>
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<tr>
<td>Renal</td>
<td>Agenesis</td>
</tr>
<tr>
<td></td>
<td>Multicystic dysplasia</td>
</tr>
<tr>
<td>Skeletal</td>
<td>Caudal regression</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Anal/rectal atresia</td>
</tr>
<tr>
<td></td>
<td>Small left colon</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Hypoplasia</td>
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</tbody>
</table>
Rehydration and correction of hyperglycaemia and electrolyte imbalance; investigation for a potential cause, such as infection, is also important. Nausea and vomiting can predispose to ketoacidosis, even with near normal blood glucose levels. The fetus is at risk of sudden intrauterine death. A compromised fetus may improve with correction in the mother's metabolic abnormality.

Hypoglycaemia can produce rapid onset of loss of consciousness and is best treated with intramuscular glucagon, as this avoids the extreme hyperglycaemia that may occur with intravenous dextrose. If dextrose is administered, 20% should be given into a vein without force.

### Gestational diabetes

Gestational diabetes is defined as carbohydrate intolerance of varying severity with onset or first recognition during pregnancy. Considerable controversy surrounds its diagnosis, significance and treatment.

The World Health Organization has defined gestational diabetes mellitus and impaired glucose tolerance two hours after a 75 g oral glucose load as more than 11 mmol/l and 8–11 mmol/l respectively. However, these criteria were based on a nonpregnant population and because of the slowed response to a glucose load in pregnancy, particularly in the third trimester, this may lead to over diagnosis. Following an abnormal glucose tolerance test, many advocate dietary advice and further blood glucose monitoring before considering insulin treatment.

The American Diabetes Association and the American College of Obstetricians and Gynecologists have endorsed the use of a 50 g oral glucose load at 24–28 weeks of gestation. A glucose level of 7.8 mmol/l or more warrants a full diagnostic oral glucose tolerance test. Despite having the greatest sensitivity (79%) and specificity (87%) of the screening tests available, it is probably best reserved for high risk rather than general populations.

Screening using glycosylated haemoglobin or fructosamine have proved too insensitive for use in pregnancy. A national survey revealed widespread variation in the choice of screening methods in UK obstetric units. A report from the Pregnancy and Neonatal Care Group of the St Vincent Task Force suggested a simpler and more cost-effective protocol, details of which are given in Table 2. However, it should be pointed out that there is no evidence base for such a protocol.

Women at increased risk of gestational diabetes include those with a family history of diabetes or personal history of gestational diabetes, those with a previously unexplained stillbirth, glycosuria or polyhydramnios and those from many ethnic minorities.

### Management during pregnancy

Throughout pregnancy, women should be monitored regularly in an antenatal diabetic clinic. They should be seen at least every two weeks until 34 weeks of gestation and then weekly until delivery. Glycaemic control should be monitored by patient records; blood glucose should be measured two or three times weekly prior to meals and snacks (i.e. six times each day). More frequent measurements should be advised when control is poor. Memory meters can be useful to monitor the correlation between meter readings and patient records. A random blood glucose level taken at the clinic visit can also provide information about control and accuracy of the patient's measurements.

### Table 2. Suggested screening protocol for gestational diabetes

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>1.</td>
<td>Check for glycosuria at each antenatal visit.</td>
</tr>
</tbody>
</table>
| 2.   | Check a 'timed random' plasma glucose:  
| a) | whenever glycosuria is detected (1+ or more)  
| b) | at booking and at 28 weeks of gestation  
| If fasting or two hour postprandial >6.0 mmol/l, or within two hours of food >7.0 mmol/l, then  |
| 3.   | Arrange a 75g oral glucose tolerance test:  
| Plasma glucose |  
| Fasting (mmol/l) | 2 hours (mmol/l)  
| Diabetes | >8 | >11  
| Gestational impaired glucose tolerance | 6–8 | 9–11  
| Normal | <6 | <9  

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Fructosamine and glycosylated haemoglobin (HbA1c) levels can give an indication of medium- to long-term glycaemic control; although some argue that indiscriminate use of these diagnostic indicators should be avoided as they are expensive and have not been shown to improve outcome.

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The woman's usual insulin regimen should not be changed if she has good diabetic control. Those with poor control should be changed to four injections per day with three pre-meal injections of short-acting insulin and one of intermediate-acting (or occasionally long-acting) insulin at bedtime.

Fetal macrosomia is related to maternal postprandial glucose levels (one-hour postprandial sugar levels being the most sensitive indicator). Therefore, one aim of treatment of diabetes in pregnancy is to reduce postprandial hyperglycaemia; this can be achieved through a combination of a diet low in simple carbohydrates and insulin therapy.

Recombinant human insulin analogues, lispro and aspart, are absorbed rapidly and achieve a faster peak insulin level, which mimics the physiological first phase of insulin release more closely than regular human insulin. Significantly lower postprandial glucose levels have been achieved in nonpregnant diabetics.16

As with conventional human insulin, recombinant analogues produce a minimal maternal antibody response, thereby minimising insulin transfer to the fetus. A retrospective analysis of 76 women with type 1 diabetes concluded that pregnancies managed with recombinant human insulin analogues have similar outcomes to those of similar diabetic populations.17 Although rapid insulin analogues have not yet been licensed for use in pregnancy in the UK, there does not appear to be any reason why women who become pregnant while using them should not continue with this regimen.

Fetal surveillance

Serial ultrasound scans, ideally performed every four weeks until 32 weeks of gestation and fortnightly thereafter, provide information about fetal growth and the presence of polyhydramnios and macrosomia. The abdominal circumference at 28–29 weeks of gestation has been shown to be predictive of subsequent macrosomia. Excess growth apparent at this gestation highlights the need for optimisation of glucose control and close surveillance during the third trimester. The relationship between diabetic control and fetal growth is not, however, entirely straightforward, as macrosomic babies can be born to mothers with apparently excellent glycaemic control. Maternal obesity is also a risk factor for macrosomia. Fat reduces insulin sensitivity, making avoidance of obesity in those with gestational diabetes especially important.

There has been some concern about the possible effects of glycaemic changes on the fetal heart rate and its computer analysis,18 although a more recent study found no significant differences in fetal heart rate parameters in relation to prandial glycaemic changes.19

The fetal biophysical profile has been shown to be of value for monitoring fetal wellbeing in diabetic pregnancies20 and is thought by some to be the single most useful means of assessing fetal wellbeing in late pregnancy in diabetic women.13

Uterine artery blood flow is not affected by diabetic glycaemic control, nephropathy or vasculopathy. If there is increased impedance to flow, this is predictive of increased risk of pre-eclampsia and/or intrauterine growth restriction, as in women without diabetes.

Fetal Doppler measurements are of limited value in pregnancies complicated by maternal diabetes mellitus as this condition does not produce the redistribution of fetal blood flow that occurs in cases of intrauterine growth restriction. Metabolic abnormalities may, however, produce acidemia without hypoxia and the diabetic fetus may be compromised while recording apparently normal fetal Doppler measurements; hence, these may be misleading.31

Obstetric complications

Pre-eclampsia is twice as common in diabetic pregnancies and the risk is correlated with the degree of glycaemic control.

Polyhydramnios occurs in about 15% of diabetic pregnancies and is again related to glycaemia: polyhydramnios generally reduces as diabetic control improves. The excess fluid is thought to be caused by fetal osmotic diuresis secondary to hyperglycaemia.

Preterm labour occurs in up to 20% of diabetic pregnancies. Ritodrine, the conventional tocolytic in the UK, produces hyperglycaemia and, particularly when used in combination with antenatal steroids, can make glycaemic control difficult to maintain. A sliding scale involving high doses of insulin is often required. It may be
that treatments other than sympathomimetics are more appropriate choices for tocolysis because of fewer effects on glycaemic control. Guidelines from the RCOG also advise that the use of antenatal steroids in pregnancies complicated by diabetes is uncertain; in view of the adverse effects of maternal hyperglycaemia on fetal lung maturation it is possible that any benefit of corticosteroids could be offset by corticosteroid-induced hyperglycaemia. Caution is therefore advised.

**Delivery**

In women with good diabetic control and an uncomplicated pregnancy it should be possible to reach 39 completed weeks of gestation. Beyond this time there is little evidence of benefit and some evidence of harm. Poorly controlled diabetes may require earlier delivery but this will increase the risk of neonatal respiratory distress syndrome and jaundice.

The mode of delivery is dependent upon a number of factors including parental choice, past obstetric history, estimates of fetal weight, prediction of asymmetrical macrosomia and fetal wellbeing. Spontaneous vaginal delivery should be the method of choice for all women with diabetes, wherever possible. In reality, the average caesarean section rate for these women in the UK is around 60%.23

A plan for delivery should be formulated at 36 weeks of gestation, or earlier in pregnancies with marked asymmetric macrosomia because of the greatly increased risk of shoulder dystocia even with premature deliveries after 34 weeks.

**Management in labour**

Diabetic control in women treated with insulin should be maintained throughout labour using an intravenous regimen of dextrose and insulin. Normoglycaemia is important because high glucose levels prior to delivery predispose to neonatal hypoglycaemia. Adequate analgesia is also vital since pain stimulates catecholamine release, leading to glycogenolysis and hyperglycaemia. There is an increased incidence of fetal distress in labour and continuous monitoring of the fetal heart rate is recommended. Experienced midwifery and obstetric staff should monitor the labour and be alert to slow progress.

**Postnatal management**

Breastfeeding should be encouraged. Insulin requirements fall to prepregnancy levels within the first 24 hours after delivery. In those with gestational diabetes, the sliding scale can be discontinued once the woman has started eating. In those with continuing diabetes, it is usual to resume prepregnancy insulin doses. However, a slightly reduced dose of two-thirds the prepregnancy levels may be indicated if the woman plans to breastfeed. There is much less need for tight diabetic control postpartum compared with pregnancy and it is important to avoid hypoglycaemia.

**Neonatal care**

Neonatal complications of maternal diabetes are shown in Table 3. All are related directly or indirectly to hyperinsulinaemia. Respiratory distress syndrome appears to be secondary to suppression of surfactant production by type-2 alveolar cells in the lung caused by excess insulin. Polycythaemia is probably due to increased hepatic erythropoiesis; this can lead to jaundice and increased blood viscosity and is a risk factor for thrombosis (most notably renal vein thrombosis). Insulin suppresses microsomal enzymes and this immaturity inhibits the ability of the liver to conjugate bilirubin, hence the risk of kernicterus is increased.

### Table 3. Neonatal complications of maternal diabetes

<table>
<thead>
<tr>
<th>System</th>
<th>Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic</td>
<td>Hypoglycaemia</td>
</tr>
<tr>
<td></td>
<td>Hypocalcaemia</td>
</tr>
<tr>
<td></td>
<td>Hypomagnesaemia</td>
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<tr>
<td>Lung</td>
<td>Respiratory distress syndrome</td>
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<tr>
<td></td>
<td>Transient tachypnoea of the newborn</td>
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<tr>
<td>Cardiovascular</td>
<td>Cardiomyopathy</td>
</tr>
<tr>
<td></td>
<td>Cardiac septal hypertrophy</td>
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<tr>
<td>Liver</td>
<td>Kernicterus</td>
</tr>
<tr>
<td>Renal</td>
<td>Renal vein thrombosis</td>
</tr>
<tr>
<td>Haematological</td>
<td>Polycythaemia</td>
</tr>
</tbody>
</table>
Six-week check

All women should be seen for a six-week postnatal check at the hospital. All those who developed gestational diabetes requiring insulin should have a glucose tolerance test performed between six weeks and three months post-partum. It may be that an abnormal test in pregnancy has uncovered previously undiagnosed type 2 diabetes rather than just 'gestational diabetes'. Even those with normal results at this time should be made aware of their lifetime risk of developing type 2 diabetes and advised to avoid excess weight gain and to take regular exercise. With regard to contraception, modern day low-dose combined oral contraceptives are generally considered safe for those with type 1 diabetes. Other options include the progesterone-only pill or the Mirena® (Schering Health) intrauterine system.

Conclusions

The discovery of insulin transformed the prognosis for women with juvenile onset diabetes. Compared with the beginning of the last century, such women can now expect a vastly improved lifespan and reproductive success. However, the St Vincent Declaration suggests that significant improvement of the management of both pre-existing and gestational diabetes need to be made if pregnancy outcome is to be comparable to those without diabetes.

References