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Diabetes mellitus

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Preconception counseling and care is as important for women with type 2 diabetes as it is for those with type 1, as the Confidential Enquiry into Maternal and Child Health (CEMACH) study of 2002–2003 (reported 2005) has shown poor outcomes in both groups[1]. However, the focus of care is slightly different in the two groups and always needs to be individualized. Diabetes is a common condition, which affected 3.75% of the population of the UK in 2006–7[2].

The increasing prevalence of type 2 diabetes mellitus among younger individuals is reflected in women of reproductive age. In our own combined obstetric and diabetes clinic no women with type 2 diabetes were encountered until 2003. However, by 2007 they accounted for 21% of the clinic population. The circumstances in our institution reflect the changes taking place in the general population, as also shown in the UK Northern Diabetes Pregnancy Survey, which recently reported a fourfold increase in the number of pregnancies in women with type 2 diabetes when they compared data for 2002–2006 to those obtained between 1996 and 2001[3].

In an ideal world women with diabetes will have planned pregnancies and the opportunity for appointments before stopping contraception, and for preconception counseling and care with a multidisciplinary team that includes a diabetes nurse and dietitian in addition to an obstetrician and diabetes physician. Although the evidence is clear that pre-pregnancy planning is beneficial for these women, at present a high percentage of pregnancies in the UK are unplanned[4,5]. As a result, many women with diabetes do not receive optimal pre- and early pregnancy care, leading to an adverse effect in 51% of those in the 2006 CEMACH study reporting unplanned pregnancy[6].

Pre-pregnancy assessment of women with diabetes allows the following areas, discussed below, to be addressed:

- Glycemic control
- Insulin analogues
- Drugs
- Complications of diabetes
- Effect of pregnancy on diabetes
- Breastfeeding
- Effect of diabetes on pregnancy
- Effect of diabetes on the neonate.
- Risks of inheriting diabetes.

GLYCEMIC CONTROL

For women with diabetes mellitus, an elevated glycated hemoglobin (HbA_{1C}) is associated with increased risks of adverse pregnancy outcome including miscarriage, congenital anomalies and stillbirth. Because these risks increase when the HbA_{1C} rises above 7% in the preconception and early pregnancy period[7], women are encouraged to achieve as near normal glycemic control as possible, with the

recent National Institute for Health and Clinical Excellence (NICE) guidelines suggesting a target preconception HbA_{1C} of 6.1%[8]. The American Diabetes Association (ADA) recommendations for care recommend a target HbA_{1C} of less than 6.0%[9]. Suhonen and co-workers report a relative risk for fetal malformations of 3.0 for women with type 1 diabetes with marginally elevated HbA_{1C} (5.6–6.8%)[10], with the association still present after adjusting for other factors including maternal age, duration of diabetes, parity and smoking. Another study stratified women with type 1 diabetes into two groups based on an initial HbA_{1C} above or below 7.5% and found a four-fold increase in adverse outcomes along with a nine-fold increase in congenital anomalies in the group with higher HbA_{1C}[11]. Although the 1989 St Vincent Declaration aimed for 'a pregnancy outcome in the diabetic woman that approximates to that of a non-diabetic woman'[12], the 2005 CEMACH data documented much higher rates of stillbirth, perinatal death and neonatal death than national rates for diabetic women in the UK, with equally poor rates being observed for types 1 and 2[1]. These findings underscore the compelling need for further improvement in outcomes.

NICE recommends that conception be avoided if glycemic control is very poor as indicated by an HbA_{1C} of greater than 10%[8]. This recommendation is based on the marked increases in congenital anomalies that accompany increases in HbA_{1C}. For example, Greene and colleagues reported a more than 12-fold increased relative risk of a congenital anomaly associated with an HbA_{1C} of greater than 12.7% compared with below 9.3%[13]. Accompanying this, significantly higher rates of spontaneous abortion also are observed once the HbA_{1C} is greater than 12%[14].

Preconception counseling and care *per se* are associated with improved outcomes for diabetic women. In a meta-analysis the rate of congenital anomalies was 2.1% in women who received preconception care in comparison to 6.5% in those who had not[5]. However, these data need to be interpreted carefully, as women who access preconception care tend to be older, less likely to smoke and have a lower HbA_{1C} in the first trimester. In contrast, those women who do not access preconception care are more likely to have had an unplanned pregnancy with its inherent risks.

One of the major components of preconception care is achieving and continuing to maintain optimal glycemic control, whilst taking into account each individual's situation with regards to her diabetes. To achieve the HbA_{1C} target recommended by NICE, the blood glucose ranges should be 3.9–5.5 mmol/l premeals and up to 7.8 mmol/l on a 1-hour postprandial reading[8]. Monitoring for postprandial hyperglycemia clearly improves pregnancy outcome[15]. Multiple daily blood glucose testing is essential to achieve the best possible glycemic control. In striving for near normal glycemic control prior to conception, it is essential that this be balanced against the risks of hypoglycemia and, in particular, severe hypoglycemic episodes. A severe hypoglycemic episode is described as one that requires assistance of another person. *A diabetic woman's risk factors for severe hypoglycemic events include previous severe episodes and known impairment or absence of hypoglycemic warnings*[16,17]. Hypoglycemia treatment and avoidance are discussed below. For those women who may be unable to achieve these extremely tight targets for whatever reasons, it is useful to be aware that each 1% reduction in HbA_{1C} achieved before conception is associated with improvements in outcome. Achieving an HbA_{1C} of below 7% without driving it lower may be more feasible for many women with longstanding diabetes, especially those on insulin[7].

For women with type 2 diabetes, it may be necessary to consider a transfer to insulin therapy to optimize their glycemic control before conception. Metformin is not licensed in the UK for use in pregnancy, but its continuation should be considered in those women

who are likely to have continued benefit from this agent, e.g. those with known insulin resistance or those likely to be insulin resistant due to obesity. This position is supported by the 2008 NICE guidelines and requires clear documentation of informed consent with respect to continued use of metformin during pregnancy[8]. Care should be taken to avoid sudden discontinuation of metformin without substitution with insulin if this results in hyperglycemia in early pregnancy. If good glycemic control can be achieved with metformin in combination with lifestyle measures (diet and exercise), then insulin initiation may not be necessary preconception, although the woman should be informed that she is likely to require insulin therapy during the pregnancy. Women with a body mass index greater than 27 kg/m^2 should see a dietitian if they have not already received dietary advice[8]. All diabetic women should be encouraged to take regular exercise both before and during pregnancy.

Sulfonylureas are usually avoided during pregnancy, although they are increasingly being used in gestational diabetes mellitus and are reported as being safe[18]. However, the usual practice in the UK is that they are discontinued and insulin substituted prior to pregnancy. All other oral antidiabetic agents should be stopped prior to conception, including thiazolidinediones (glitazones), meglitinide analogues, alpha-glucosidase inhibitors, GLP-1 analogues and gliptins. Transfer to insulin should be arranged promptly in the case of unplanned pregnancy in a woman with type 2 diabetes mellitus taking any of these agents, as their safety has not been formally assessed in pregnancy. In the absence of safety data, some people still use these agents.

INSULIN ANALOGUES

Insulin analogues were developed in an attempt to achieve similar pharmacokinetics following an insulin injection to those achieved with endogenously produced insulin. As insulin affects growth and gene expression in addition to having metabolic actions, the safety of insulin analogues has been studied carefully and their use in pregnancy has been approached with caution.

The rapid acting analogues insulin lispro and insulin aspart have advantages over conventional short-acting human insulin due to their shorter onset of action, earlier peak effect and reduced likelihood of hypoglycemic events due to their shorter duration of action[19]. These attributes make them ideal for use in pregnancy, as they can help avoid postprandial hyperglycemia combined with a lower risk of hypoglycemic events. Both lispro and aspart have similar outcomes in pregnancy in comparison with human insulin, with improved satisfaction and potential benefits with respect to observed hypoglycemia; their use in pregnancy is supported by both NICE in the UK and the American Diabetes Association (ADA) in the US[8,9,20,21].

This position is in contrast to that of the long-acting insulin analogues: insulin glargine and insulin detemir. Current guidelines (2008) from both NICE and ADA are that women should be transferred to isophane insulin, commonly known as NPH (neutral protamine Hagedorn) by the time of the first antenatal visit. These recommendations are made primarily because of insufficient patient safety data, although evidence is beginning to accrue supporting their use. Long-acting insulin analogues were designed to provide a longer duration of action with a less pronounced peak of action compared to isophane insulin. Insulin glargine and insulin detemir both have a duration of action of up to 24 hours[22,23]. Price and associates reported a group of 32 women treated with insulin glargine compared to matched controls treated with human insulin with no observed differences in birth weight, fetal macrosomia or neonatal morbidity[24]. A clinical trial comparing insulin detemir to isophane insulin in 400 pregnant women

with type 1 diabetes is currently in progress with an estimated completion date in 2010[25]. Women who have had previous problems with isophane insulin, especially nocturnal hypoglycemia, may be reluctant to transfer back to isophane insulin from a long-acting analogue insulin. In this situation, it may be appropriate to continue the analogue insulin if an informed decision is made balancing the benefits of improved glycemic control with less hypoglycemia versus an unquantified risk to the fetus.

DRUGS

Women with diabetes often take a range of medications prior to pregnancy. Ideally a preconception appointment with a multidisciplinary team allows these medications to be reviewed so that appropriate changes can be planned before conception occurs. Unfortunately, many conceptions are unplanned and this is not always possible.

From 1 to 6% of women of childbearing age have clinically diagnosed hypertension prior to pregnancy and are taking antihypertensive medication(s); many also have long-term diabetes[26]. In addition, many non-hypertensive diabetics are prescribed angiotensin-converting enzyme inhibitors (ACE inhibitors) for diabetic nephropathy. Ideally such drugs should be reviewed prior to conception to determine whether they should be continued, stopped or changed prior to pregnancy, or once it is confirmed. Parkinson reviewed the safety of antihypertensive drugs in pregnancy and concluded that there was no evidence of teratogenicity with methyldopa, beta-blockers, calcium channel blockers and hydralazine[27]. It is well known that ACE inhibitors are absolutely contraindicated in the second and third trimesters because they are known to cause fetal oliguria, which leads to oligohydramnios and its sequelae for the fetus[28]. Case reports suggest similar fetotoxicity with angiotensin II receptor antagonists, and animal studies have shown that angiotensin II receptor antagonists are associated with serious fetal anomalies[29]. A recent American study also suggested a teratogenic effect for ACE inhibitors: 7.12% of fetuses born to women taking ACE inhibitors at the time of conception had anomalies at birth compared to 2.63% of the population not exposed to antihypertensive medication in the first trimester[30]. Under these circumstances, women taking ACE inhibitors or angiotensin II receptor antagonists at the preconception assessment should be assessed to determine whether they should stop medication whilst trying to conceive or change to alternative drugs at this time. It is the authors' practice to continue all other antihypertensive medications whilst women are trying to conceive, then to review the need for continuation during pregnancy depending on the blood pressure at that time. When the midtrimester drop in blood pressure occurs, many hypertensive women do not need to continue treatment, but may need reinstitution later in the pregnancy. The usual practice in the UK is to use methyl dopa or labetalol for blood pressure control as these are the medications with which British obstetricians have the most experience.

Many diabetic women are prescribed statins to provide long-term protection against cardiovascular disease. Unfortunately, data on the use of statins in pregnancy are limited, and the manufacturers advise against their use at this time. However, the available evidence is far from conclusive, but since statin use is preventive rather than therapeutic the most sensible approach is to advise women to stop these drugs when they are planning to conceive and to restart them once they have finished breastfeeding[31].

Because folic acid supplements decrease the risk of neural tube defects (NTDs) and facial clefts, it is recommended that all (as opposed to only those who are diabetic) women take them for 3 months before stopping contraception and until 12 weeks into the pregnancy[32,33].

Many authorities, especially those in the US, recommend continuing folic acid throughout the remainder of the pregnancy. The need for the preconception administration is because the neural tube is closed by the 28th day of gestation and commencing folic acid after that date is without benefit, a fact which is often underappreciated in the wider medical community. The standard recommended dose of folic acid is 400μg/day, but women at high risk of NTDs are advised to take a higher dose (5 mg daily), leading to the NICE recommendation that women with diabetes take the higher dose[8].

Women with long-term diabetes are at greater risk of developing pre-eclampsia than the general population (see below), a point which favors prophylaxis to reduce the risks of this condition[34,35]. Unfortunately, the ideal agent to accomplish this task has not yet been determined[36]. Low-dose aspirin was investigated in the CLASP study and found to only slightly reduce the rate of pre-eclampsia[37]. A subsequent meta-analysis on the use of prophylactic antiplatelet agents (mainly low-dose aspirin) suggested a 10% decrease in relative risk of developing pre-eclampsia[38] and confirmed the safety of low-dose aspirin in pregnancy. If low-dose aspirin is to be used, it should be started once a woman has a positive pregnancy test and continued until 34 weeks, as per the CLASP protocol. Whereas the initial investigation of prophylactic high-dose vitamins C and E (antioxidants) appeared to protect against pre-eclampsia, the VIP trial did not confirm this, and showed some significant negative effects[39,40]. Calcium supplements are currently being investigated, and the results appear to be encouraging. A recent meta-analysis of 12 randomized controlled trials of calcium supplements showed a 52% reduction in the incidence of pre-eclampsia compared to placebo with no obvious evidence of harm[41]. The benefits appeared to be even greater in high-risk groups. At present in the UK, calcium supplements are not often used in clinical practice.

The prevention of toxemia is a complex issue and is discussed elsewhere in this volume.

COMPLICATIONS OF DIABETES

Preconception consultations are an ideal time to assess any diabetic complications along with working to achieve improved metabolic control. Baseline measurements of renal and thyroid function should be taken. As autoimmune thyroid disorders are more common in women with type 1 diabetes and even mild anomalies in thyroid hormone levels can impact early fetal development, it is essential to identify those requiring treatment[42].

Retinopathy

Diabetic retinopathy is a broad term encompassing all disorders of the retina caused by long-term high blood glucose levels. It is essential for all women with diabetes to have a retinal assessment prior to conception to determine whether ophthalmological treatment is required. The initial retinal assessment also provides a baseline for further monitoring during each trimester. Pregnancy and rapid improvement of glycemic control are both known to be associated with deterioration of retinal disease, and sudden improvement of glycemic control should therefore be avoided until after a retinal assessment has been undertaken[8]. Women with proliferative retinal changes require urgent referral for ophthalmologic review and should receive treatment prior to pregnancy.

The Diabetes Control and Complications Trial[43] confirmed that diabetic retinopathy can worsen during pregnancy but it is reassuring that no long-term consequences were demonstrated when this occurred. A prospective study of 139 women with pregestational type

1 diabetes demonstrated a progression of retinopathy in 5% of pregnancies and observed that this was more likely in women with a longer duration of diabetes (>10 years) and more advanced retinal disease at baseline[44]. Women should be reassured that laser photocoagulation can be used during pregnancy, but ideally treatments should be undertaken prior to conception.

Nephropathy

Nephropathy is a serious complication of diabetes that can lead to end stage renal failure in addition to poor pregnancy outcomes (see Table 1). In a retrospective analysis of stillbirths occurring in women with type 1 diabetes, a six-fold higher incidence of nephropathy was noted in the stillbirth group compared to the reference group (i.e. those without nephropathy)[45]. Assessment of renal function with serum creatinine, estimated glomerular filtration rate (eGFR) and urinary excretion of albumin prior to conception should be performed in all diabetic women prior to conception. The 2008 NICE guidelines recommend referral to a nephrologist if creatinine is greater than 120μmol/l or eGFR below 45 ml/min[8]. Optimal control of blood glucose and hypertension protects against development or progression of nephropathy both prior to and during pregnancy. As ACE inhibitors and angiotensin II receptor antagonists are commonly used for nephropathy outside pregnancy, a careful review of medication as described above is essential.

Measurement of urinary albumin excretion prior to or early in pregnancy gives an individual baseline for comparison later in pregnancy and enables identification of those women with microalbuminuria or overt diabetic nephropathy, both of which are associated with preterm delivery, mainly due to pre-eclampsia[46]. Pregnancy does not appear to have a negative impact on long-term renal function in women with diabetic nephropathy who have maintained a good level of pre-pregnancy renal function (normal levels of serum creatinine) in contrast to those with low creatinine clearance before pregnancy[47,48].

Table 1 Diabetic nephropathy and effect on pregnancy. Adapted from American Diabetes Association summary of evidence and consensus recommendations of care for managing pre-existing diabetes for pregnancy[9]

Level of albuminuria	*Effect on pregnancy*
Normal <30 mg/24 hours	Unknown
Microalbuminuria 30–300 mg/24 hours	Increased pre-eclampsia
Macroalbuminuria >300 mg/24 hours	Increased pre-eclampsia
Protein excretion >500 mg/24 hours	Increased risk of growth restriction

Other complications of diabetes

Data regarding changes in diabetic neuropathy during pregnancy are lacking. Sensorimotor neuropathy in women with diabetes rarely causes problems during pregnancy and does not appear to progress, but careful review of drugs used for control of neuropathic pain should be undertaken during preconception appointments because of the possibility of teratogenicity. Women with autonomic neuropathy can have particular problems during pregnancy. Autonomic neuropathy is associated with hypoglycemic unawareness, which can be aggravated by pregnancy. Management of hypoglycemia is discussed below. Patients who have developed gastroparesis as a component of autonomic neuropathy often have poor metabolic control and inadequate nutrition[49,50]. This complication is subsequently associated with adverse pregnancy outcomes and may

be considered a relative contraindication to pregnancy.

Cardiovascular disease is a leading cause of mortality for women with either type 1 or type 2 diabetes. A population-based study of acute myocardial infarction (AMI) during pregnancy shows that, although this condition is rare with a rate of 6.2 per 100,000 deliveries, AMI is associated with a mortality rate of 5.1%. In this study, diabetes was significantly associated with AMI[51]. The UK Obstetric Surveillance System (UKOSS) is currently collecting data on AMI in pregnancy (personal communication, UKOSS) and this may shed more light on risk factors, including diabetes. The presence of macrovascular complications should be considered during the preconception assessment for all women with longstanding type 1 diabetes and all women with type 2 diabetes. Screening with a minimum of an ECG should be arranged, and an exercise test should be considered if other risk factors are present, such as hypertension, hyperlipidemia, smoking, family history of premature cardiac disease and diabetic nephropathy.

Eating disorders associated with diabetes can present problems with glycemic control and may result in problems during pregnancy. The possibility of disordered eating patterns, including binge eating and insulin restriction to avoid weight gain should be considered during preconception assessments.

EFFECT OF PREGNANCY ON DIABETES

Hypoglycemia

Hypoglycemia, usually defined as blood glucose of less than 4 mmol/l, is a barrier to tight glycemic control. Women need to be aware that the tight control required before conception, and in pregnancy, may predispose them to more hypoglycemic episodes. Evers and colleagues demonstrated that the frequency of severe hypoglycemia is increased by two- to three-fold during the first trimester and is associated with a history of severe hypoglycemia, more than 10 years' duration of diabetes, HbA_{1C} below 6.6% and a higher total daily dose of insulin[52]. Factors related to pregnancy that contribute to hypoglycemia include nausea, vomiting and glucose transfer across the placenta to the fetus. The risk of hypoglycemia is increased particularly between meals and overnight when the woman is fasted. This risk is in addition to the peak of action associated with the use of isophane insulin, thus making between meal and before bed snacks important. Appropriate education with a diabetes specialist nurse and dietitian is extremely helpful not only for achieving optimal glycemic control preconception, but also in preparation for the early weeks of pregnancy. Information about balancing exercise with good glycemic control should be included during this education.

Due to the increased frequency of hypoglycemia, it is vital that appropriate treatment of hypoglycemia be discussed during preconception assessments. Prompt return to normoglycemia, after hypoglycemia, may help to reduce further blunting of the counter-regulatory responses. Animal data suggest an association between hypoglycemia and congenital malformations, but this has not been confirmed in human studies[53]. It is not known if the increased rate of congenital malformations seen in women with an HbA_{1C} between 5.6 and 6.8% is due to hypoglycemia or the effects of episodes of hyperglycemia, including those that result as a rebound effect of hypoglycemia treatment[10].

First-line hypoglycemia treatment should be consumption of fast-acting carbohydrates such as glucose tablets or a sugar containing drink. Once blood glucose levels have recovered, further hypoglycemia should be avoided by consumption of longer-acting carbohydrates such as a cereal bar, fruit, biscuits or the next meal if it is due. In addition, all women on insulin should have a supply of concentrated glucose

gel (Glucogel™, a 40% dextrose gel, is commonly prescribed in the UK) and a glucagon kit[8]. As emphasized by the American College of Obstetricians and Gynecologists (ACOG) family members and, if necessary, co-workers should also be educated in the recognition and treatment of hypoglycemia[54].

Changing insulin requirements

Insulin requirements change during pregnancy with a general increase as pregnancy progresses, although this effect varies between individuals. There appears to be a triphasic pattern of insulin requirements, which remain steady in the first trimester and increase thereafter[55]. Due to insulin resistance, women with type 2 diabetes require higher doses of insulin and experience greater increases in dosage than those with type 1 diabetes. Interestingly, in a prospective study of women with type 1 diabetes, after initial increases in insulin doses a fall in insulin requirements was observed between 7 and 15 weeks' gestation[56]. These changes, in combination with the need to balance near normal glycemic control with avoidance of hypoglycemia, result in the need for intensive blood glucose monitoring throughout pregnancy.

Diabetic ketoacidosis

During pregnancy women with diabetes are more susceptible to diabetic ketoacidosis (DKA). Kamalakannan and associates reviewed contributing factors such as increased insulin resistance and pregnancy induced lipolysis, along with precipitating factors for DKA which include infection, vomiting and poor compliance[57]. Prompt diagnosis and treatment of DKA is important in pregnancy because of the potential for fetal harm. DKA often develops quickly and may be associated with less marked hyperglycemia than is usual outside of pregnancy[58]. Despite this, episodes of DKA during pregnancy are fortunately rare due to intensive monitoring and tight blood glucose control. The preconception assessment provides an opportunity to ensure that all women with type 1 diabetes have a method of checking for ketones (either via urinary stick testing or with a meter with the appropriate ketone testing strips) and should check for them if blood glucose is raised above 12 mmol/l, especially if they should feel unwell with nausea, vomiting or abdominal pain. Women should be clearly informed that if they have high blood sugar levels with ketones, or evidence of urinary ketones with even moderate blood sugar elevations, they should seek medical help urgently rather than attempting to manage the situation themselves.

BREASTFEEDING

Many women with diabetes are not aware that there is no reason why they should not breastfeed, and breastfeeding should be encouraged, in the interests of both the mother and her baby. These facts should be presented at the preconception appointment and stressed throughout antenatal care appointments. It must be appreciated, however, that breastfeeding requires an increase in calorie intake accompanied by a decrease in insulin. Accordingly, breastfeeding diabetic women should be advised to have food before or during feeding[8]. Women with type 2 diabetes should also be aware that they can continue taking metformin or glibencamide whilst breastfeeding, because there is adequate information on the safety of the low levels of metformin and on the absence of glibencamide in breast milk[8,59,60]. As data on the safety of breastfeeding with the other oral hypoglycemic agents are limited, NICE recommends that they be avoided. In practice this means that type 2 diabetics treated with these agents before pregnancy are usually advised to stay on insulin until they have

finished breastfeeding[8]. If women are taking other drugs, these too must also be considered in respect of breastfeeding.

EFFECT OF DIABETES ON PREGNANCY

Poor diabetic control has a significant adverse effect on pregnancy and is associated with an increased risk of untoward pregnancy outcomes. These possibilities should be discussed at the preconception appointment, not least because many of these effects can be modified by improving diabetic control before conception and maintaining good control throughout the pregnancy. Unfortunately both miscarriage and fetal anomalies are much more common in women with diabetes, with higher rates for both in women with poor pre-pregnancy control as reflected by the HbA_{1C} in early pregnancy (see above). However, it must be recognized, and explained to women that both miscarriage and fetal anomalies are not exclusive to pregnancies in diabetics, or those with poor control.

A comparison of miscarriage rates in 386 type 1 diabetics and 432 non-diabetic women reported a 16% miscarriage rate in both groups[61]. However, this simplistic assessment is misleading because, while there was no relationship between the miscarriage rate and HbA_{1C} level within the normal HbA_{1C} range, in the above normal range the miscarriage rates increased in an approximately linear fashion in parallel with increasing levels of HbA_{1C}. In a smaller study of 83 type 1 and type 2 diabetics, 95% of the miscarriages occurred in women with an HbA_{1C} level of more than 11.5%[62].

Suhonen and colleagues adjusted for factors including maternal age, duration of diabetes, parity and smoking, and found a relative risk for fetal malformations of only 1.6 for women with type 1 diabetes with an HbA_{1C} less than 5.6%[10]. Similarly, a comparison of type 1 diabetics with an early pregnancy HbA_{1C} above or below 7.5% demonstrated a nine-fold increase in the rate of congenital anomalies in the group with the higher HbA_{1C}[11]. The rate of fetal malformations increases even further with very high HbA_{1C} levels[13].

Because the very high rates of adverse pregnancy outcome can be improved with improved diabetic control before conception, it is absolutely essential that women with diabetes are aware of these risks before conception. They should also be provided with help to improve their control well before their first appointment in the antenatal clinic, as each 1% decrease in preconception HbA_{1C} halves the rate of adverse pregnancy outcomes[7].

Women with long-term diabetes are at greater risk of developing pre-eclampsia than the background population, and this risk is greater the longer the duration of the woman's diabetes, with a higher risk in women with pre-existing diabetic renal disease or hypertension[34,35]. Unfortunately, since both proteinuria and hypertension are common in pregnancies with long-term diabetes, it can be difficult differentiating between this phenomenon and developing pre-eclampsia. Unfortunately, these complications cannot be prevented by good glycemic control in pregnancy. Regardless, there are advantages in discussing these risks at the preconception appointment so that women are aware of potential problems and so that prophylactic treatment, i.e. low-dose aspirin (see above), can be considered and potentially started early.

Women are often aware of the risk of fetal macrosomia, leading to the birth of the classic cherubic infants of diabetics. However, they are often unaware that the risk of macrosomia (and related polyhydramnios) can be modified by good blood sugar control during the pregnancy, especially in the third trimester. The preconception appointment is an ideal time to discuss this effect of diabetes, and how it may be managed (see above). Fetal growth restriction can also complicate the pregnancies of women with diabetes and can have even greater implications for fetal outcome[6].

The CEMACH enquiry[1] showed that antenatal evidence of fetal growth restriction was associated with poor pregnancy outcome (OR 2.9, 95% CI 1.4–6.3, adjusted for maternal age and deprivation), whereas antenatal evidence of fetal macrosomia was not. Women should be reassured that fetal growth and amniotic fluid volume will be regularly assessed with serial ultrasound scans throughout pregnancy, and that decisions on pregnancy management will be directed by the scan findings. NICE recommends ultrasound scans every 4 weeks from 28 weeks' gestation[8], whereas the Australasian Diabetes in Pregnancy Society only recommends growth scans at 28–30 weeks' and 34–36 weeks' gestation[63].

Since there is increased risk of fetal and maternal trauma during delivery with macrosomia, the risks and benefits of attempting vaginal birth (possibly with induction of labor) or delivery by planned cesarean section need to be considered if macrosomia is diagnosed by ultrasound scan[8]. The CEMACH enquiry[1] reported shoulder dystocia in 7.9% of vaginal births in diabetic women, with no difference between type 1 and type 2 diabetics; but a 42.9% incidence of shoulder dystocia was reported when the baby weighed 4.5 kg, or more[6]. Despite this, it must be acknowledged that it is not possible to accurately determine fetal weight before delivery and that a significant error (8–15%) exists in fetal weight estimation by ultrasound[63]. Unfortunately, accuracy of estimated fetal weight is worse in women with diabetes and when the fetus is macrosomic[65,66]. Neither shoulder dystocia nor the possible sequelae for the fetus (Erbs palsy) can always be prevented, but awareness of the possibility and proper and timely management of the dystocia if it occurs is likely to decrease the risk of long-term complications in the baby[67]. Because of this, every maternity unit should have guidelines for the management of shoulder dystocia and should have regular drills for all labor ward staff in its management. Since the majority of macrosomic babies do not experience shoulder dystocia, the Royal College of Obstetricians and Gynaecologists (RCOG) in the UK does not recommend delivery by cesarean section with suspected macrosomia in non-diabetic women, but does recommend consideration of planned cesarean section in diabetic women because of the relatively high rates of shoulder dystocia[67]. This recommendation is endorsed by both ACOG and NICE[8,54,68].

Induction of labor does not decrease the maternal or neonatal morbidity of shoulder dystocia but does decrease the risk of a large for gestational age (LGA) baby and the incidence of shoulder dystocia. Therefore, ACOG expressly advises against induction of labor for suspected fetal macrosomia[54]. A randomized controlled trial of 200 women with insulin-requiring diabetes (mainly gestational diabetes) and a case–controlled study of 260 diabetics both compared induction of labor at more than 38 weeks' gestation with expectant management[69,70]. Both studies found an increase in the rates of LGA babies and shoulder dystocia in the expectant management group, with no increase in cesarean section rates in the induction group. NICE therefore recommends induction of labor after 38 completed weeks in diabetics[8]; this differs from the advice of the Australasian Diabetes in Pregnancy Society which is that induction of labor should 'only be considered for obstetric and/or fetal indications'[62].

Unheralded intrauterine death remains a significant contributor to perinatal mortality in pregnancies complicated by diabetes mellitus. Unfortunately, conventional tests of fetal well-being are poor at predicting these events[8]. The CEMACH investigation of current (2002/2003) UK management of pregnancy in diabetics reported a stillbirth rate of 26.8 per 1000 births (95% CI 19.8–33.8 adjusted for maternal age), with 27.6% of these stillbirths occurring after 37 weeks[1]. Women may be aware of this statistic before they conceive and need to be reassured that the rate is fairly low

in women with well controlled diabetes. It has long been common practice to advise women with diabetes that delivery should occur early because of the risk of unexpected stillbirth; as noted above, NICE advise delivery after 38 completed weeks[8].

The 2005 CEMACH report[1] on 3808 pregnancies in women with diabetes in 2002/2003 showed that women with diabetes have fairly high rates of induction of labor (39%) and cesarean section (67%). Ideally women will be aware of these data before they conceive, but it is equally important that they are aware that neither is inevitable! In the UK the rate of induction of labor is of course higher in this group of women, as it is advised that even with well controlled diabetes delivery should be considered after 38 weeks (see above)[8]. Although the 2005 CEMACH report showed a UK cesarean section rate of 67% in women with diabetes compared to 24% in the non-diabetic population[1], this high rate is not inevitable as shown by the cesarean section rate at our hospital in women with pre-existing diabetes (40% in 2006 and 42% in 2007).

EFFECT OF DIABETES ON THE NEONATE

Even before conception women worry about the effect their diabetes may have on the newborn baby. It is thus appropriate to briefly discuss neonatal management during preconception counseling. In particular, women should be reassured that, although the babies of diabetic women require careful monitoring and should therefore be delivered in a unit with appropriate neonatal facilities, many newborns experience no serious problems and stay with their mothers in the neonatal period, as recommended by NICE[8].

Diabetes of all types is a recognized risk factor for neonatal hypoglycemia, and, though less likely, can still occur in the babies of mothers with well controlled diabetes. In a study on the frequency, risk factors and long-term effects of neonatal hypoglycemia, 9.18% of the 1023 babies admitted to the neonatal unit were hypoglycemic; of these, 34.1% were born to diabetic mothers[71]. An audit from the National Women's Hospital, New Zealand, showed that of the 136 babies of diabetic mothers admitted to the neonatal unit the indication for admission was hypoglycemia in 51% of cases[72]. Another study compared 78 women with rigorously controlled diabetes and 78 controls; these authors noted neonatal hypoglycemia in 14% of the neonates of diabetic mothers compared to 1% of the controls[73]. As monitoring for and good management of hypoglycemia is very important, every maternity unit should have written guidelines for blood sugar management of the neonates of diabetic women[8]. Women require reassurance that good control can often prevent neonatal hypoglycemia, and that early feeding (preferably breastfeeding), followed by feeding at frequent intervals, will help the baby maintain its blood glucose levels[8]. Neonatal blood glucose testing, preferably after feeding, routinely should be carried out 2–4 hours after birth. Ideally babies of women with diabetes should be kept with their mothers, and every attempt should be made to control the babies' blood sugar without resort to parenteral glucose (which would require admission to the neonatal unit), though this should obviously be considered if the babies blood glucose level does not improve with less invasive measures[8].

Polycythemia, hyperbilirubinemia, hypomagnesemia, previously unrecognized congenital heart disease and cardiomyopathy are all more common in the babies of women with diabetes, but all are rare, especially if the diabetes is well controlled in pregnancy and the baby is delivered at or near term. Screening should therefore only be recommended in babies with clinical signs[8]. So that the babies of diabetic mothers can be monitored for rare neonatal complications, and to ensure that the baby is maintaining its blood glucose levels

and has established a good feeding pattern, transfer to community care should not occur before the baby is 24 hours old[8].

RISKS OF INHERITING DIABETES

The risk of the child inheriting diabetes is a frequently asked question. For parents with type 1 diabetes this risk is higher for children of diabetic men (6%) than women (1.3%); for parents with type 2 diabetes, the risk is 15% for one first-degree relative rising to greater than 60% if both parents have type 2 diabetes[74]. Interestingly, there is a higher risk for developing type 2 diabetes if the mother is affected compared to the father, suggesting that the intrauterine environment may be a predisposing factor and possibly indicating that there could be benefits of intensive glucose control that extend beyond pregnancy[75].

SUMMARY

Optimal management of diabetes mellitus is important throughout pregnancy and ideally starts prior to even starting attempts to conceive. The evidence above demonstrates how essential this is to improve each woman's chance of a good pregnancy outcome.

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