Type 1 and type 2 diabetes and pregnancy

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Summary  Types 1 and 2 diabetes in pregnancy present multiple challenges to healthcare groups. Although there are debates regarding the precise pathophysiology of the different complications of diabetes during pregnancy, there is increasing evidence that good pre-conception and early pregnancy glycaemic control will reduce the rate of all complications, including macrosomia. The relationship between malformation and blood glucose levels may differ for different malformations.

The provision of organised pre-pregnancy care for this group allows an opportunity to reinforce the need for tight glycaemic control, commence vitamin supplementation, identify those with complications of diabetes who require more specialist evaluation and preparation, and to inform women of pregnancy risks. How this type of detailed care is provided is a major organisational issue for all healthcare systems. Current UK provision falls short.

Many interventions and strategies during pregnancy, including the degree of glycaemic control, have a poor evidence base. Short-term variation of glucose values across the day may contribute to morbidity in apparently well-controlled diabetes. Novel strategies will be required to reduce this. The demands on pregnant women with pre-conception diabetes should not be underestimated.

Introduction

Type 1 diabetes complicates 1 in 300 pregnancies, and there has been a 50–70% increased incidence of type 1 diabetes in women in the childbearing age range over the last 20 years. In recent years, type 2 diabetes has emerged as a significant problem.

In one US study, two-thirds of pregestational diabetes was type 2, and recent UK data suggest rates of 30–40%. The prevalence is dependent on ethnic mix. This population rate is set to rise with continuing concern about childhood obesity and it appears to be moving into an earlier age range.
Pathophysiology

Despite the advances in diabetic care and perinatal care, pregnancy outcome for general populations of pregnancies with type 1 diabetes is substantially worse than that of the normal population. Outcomes from recent population studies demonstrate the main problems (Table 1). As more reports emerge examining type 2 diabetes, it is clear that outcomes are similarly poor.

Intrauterine death

Although late intrauterine death is more likely in poorly controlled diabetes, and in macrosomic fetuses, it can occur in any diabetic pregnancy. Traditionally it occurs in the final 4 weeks of pregnancy, though the Mersey data set does not support this for type 1 diabetes. Reported rates for type 2 diabetes are similar though large population datasets are few. Some studies of type 2 diabetes have suggested higher mortality rates than for type 1, argued as a consequence of an older, more parous, and more obese group where a substantial proportion of women are from ethnic groups for whom access to healthcare is acknowledged as difficult.

The precise reason for these deaths is unclear. Some, seen in diabetic women with existing vascular disease, are related to placental vascular disease, and the pathophysiology is that seen in idiopathic or pre-eclamptic intrauterine growth restriction. The more usual death of a well-grown or overgrown fetus is less easily explained. There is evidence that the fetus of a type 1 diabetic women has an average blood oxygen level around the 10th centile, and that a higher proportion are chronically hypoxic. Cord erythropoietin levels are increased and chorionic villous membrane thickness is increased in the placentas of diabetic pregnancies, both known phenomena secondary to hypoxia. Hyperinsulinaemia increases fetal oxygen consumption and will reduce blood oxygen values. Maternal hyperglycaemia may alter red cell oxygen release.

The fetus of a diabetic mother appears to be more likely to have a low pH and high lactic acid in the face of normal or mildly hypoxaemic blood oxygen values. This seems to be related to fetal insulin levels. Ketoacidosis reduces uterine blood flow and in experimental animal models infusions of ketone bodies result in hypoxaemia. Vasculopathy may affect the uteroplacental vasculature. What is even less clear is the timing and speed of these changes, as many deaths have been described within 24–72 h of reassuring fetal monitoring tests that should detect fetal hypoxia.

Fetal abnormality

Rates of malformation have been reported as 60 per 1000 from Scotland, 63 per 1000 from Finland, 84 per 1000 from the Mersey and 88 per 1000 from the Netherlands. Type 2 diabetes rates where measured appear similar to those of type 1, being 44 per 1000 in New Zealand and 99 per 1000 in the West Midlands.

There is a wide variation in the type of abnormality seen in diabetic pregnancies, but it would appear that the teratogenic insult must function prior to 8 weeks gestation (3–6 weeks post-conception). Cardiac, neural tube, genitourinary and skeletal malformations represent the common findings. Within the cardiac defects found there appears to be an overrepresentation of great vessel abnormalities.

The relationship between poor diabetic control, however measured, and the fetal abnormality rate is clearly documented. However, the lack of an absolute relationship has hampered exploration of the precise pathophysiology. Conventional belief has been that teratogenesis is related to hyperglycaemia during the key period. More recent laboratory work has suggested a more complex relationship between maternal and fetal fuel metabolism. There are direct genotoxic effects from abnormal fuels, or disruption of cellular signalling. Hyperglycaemia directly alters yolk sac development and differentiation, thought to be a common pathway for many teratogens. Hypergly-

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<th>Pregnancy outcome in diabetes.</th>
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<td>Miscarriage</td>
<td>13%</td>
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<td>Malformation</td>
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<td>Stillbirth</td>
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<td>Perinatal mortality</td>
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caemia is also capable of altering free radical scavenging systems via changes in inositol, prostaglandin synthesis and direct stimulation, resulting in increases in free oxygen radicals that can be teratogenic. There is now convincing evidence in experimental animals that hyperglycaemia affects the Pax-3 gene central for neural tube closure. This appears to be a combination of a direct genotoxic effect and the effect of changes in reactive oxygen species. It can be reversed by the use of free radical scavengers such as vitamin E. Similar theories have been advanced for renal malformations in diabetes.

Hypoglycaemia has been repeatedly implicated in animal models, though human observational studies have consistently failed to find a link. Of particular interest are the effects of hypoglycaemia on the embryonic heart. There are changes in morphology, intramyocyte lactic acid levels, and in regulatory proteins and hormones. This raises the possibility that in diabetes, different malformations may arise through different issues of glycaemic control.

The duration and timing of exposure to potential teratogenic stimuli may play a role. Animal models suggest that very short exposures at key times will result in specific abnormalities, and that the precise magnitude of the aberrant fuel levels may also be crucial. This proposed model might explain why some apparently well-controlled women have a fetus with an abnormality.

Macrosomia

The median birth weight ratio for infants of type 1 diabetic mothers is shifted to the left with values between 1.21 and 1.57 described. Using conventional definitions of macrosomia, between 35% and 70% of infants are macrosomic in series of either type 1 or 2 diabetes. There is general organomegaly, increased muscle mass, and increased adiposity. The increased adiposity appears to be secondary to fat cell hyperplasia.Bone growth does not appear to be altered. Fetal hyperinsulinaemia appears to be the primary factor. Cord insulin, C peptide and leptin levels are increased in macrosomic fetuses. Amniotic fluid insulin is elevated in advance of any change in growth in those fetuses destined to be macrosomic. Other than maternal body mass index, only maternal levels of IGF-1 and IGF-2 have been linked to ultimate birth weight.

Reduction in mean blood sugars using various control regimens has uniformly been linked to a reduction in the proportion of macrosomic infants. Although data are scanty, there is a suggestion that using postprandial glucose values results in less macrosomia.

The timing of this excessive fetal growth is early. Ultrasound studies show that accelerated growth is detectable in the late second trimester, and studies of indices of control suggest that very tight control after this may not influence birth weight. The most recent examination of both types 1 and 2 diabetes demonstrated significant differences in fetal abdominal circumference at 18 week's gestation in those fetuses born with macrosomia. Given the presumed lack of sensitivity of the fetal adipose system to fetal insulin in mid-pregnancy, this does suggest that factors other than hyperglycaemia and hyperinsulinism have a role. These include impaired responses of other counter regulatory hormone control systems to episodic hypoglycaemia, suggesting that too tight control may not be entirely beneficial. There may also be a fetal component, as different fetuses may have different thresholds of maternal glucose levels at which they develop hyperinsulinaemia. These other factors may explain the failure to link indices of control, such as glycated haemoglobin at any gestation, with ultimate birth weight centile.

Respiratory distress

The risk of respiratory distress is increased six-fold, though this may be altered through good glycaemic control and delay in delivery. Hyperglycaemia and hyperinsulinaemia delay fetal lung maturation. They may interfere with uptake of choline and glucose into type II pneumocytes, incorporation of substrates into surfactant proteins, and cortisol's role in the timing of surfactant production. The latter may be by direct inhibition of key enzymes, or by interfering with the initiation of promoter substances. Intriguingly, fetuses of women who have episodes of severe hypoglycaemia during pregnancy have been shown to have more mature lungs at 32–34 week's gestation.

Neonatal hypoglycaemia

Hypoglycaemia in the neonatal period has been reported in 20–70% of infants in both types 1 and 2 diabetes, though symptomatic hypoglycaemia is now rare.

The mechanism is dependent largely on glycaemic control in labour. Prior poor control will have caused fetal hyperinsulinaemia with islet cell hyperplasia, and there is support for this hypothesis.
from cord insulin and C-peptide studies. Continuing high levels of insulin release will drive blood sugar levels down. The effect can be modified by intrapartum control, as fetal glucose values reflect immediate maternal values.

**Pre-pregnancy care**

The relationship between diabetic control and fetal abnormality, and the gestation of teratogenic insult, demonstrate that the achievement of tight glycaemic control in the peri-conception period is key. Work in the 1970s, led by the Edinburgh group, demonstrated an ability to reduce malformation rates to near the population norms if women attended for targeted pre-pregnancy diabetic care. Several groups over the years have confirmed these observations, including an analysis of women who became pregnant in the DCCT study, where those randomised to the stricter control arm had a significantly lower rate of fetal malformations. Systematic review of available evidence has demonstrated a mean reduction in glycated haemoglobin of 2–3% in those attending for preconception care, and a two-thirds reduction in malformation rates.

**Organisation of care**

There is little guidance on what constitutes adequate pre-pregnancy care. An illustrative service model from the UK Diabetes National Service Framework suggested that there should be a separate clinical service run jointly by obstetric and adult diabetes services. The American Diabetes Association, in its 2003 position statement, laid out very detailed advice on what it considered should be included in pre-conception care. In the report on the organisation of maternity services for diabetic women in the UK, less than 1 in 5 services offered care that might have met either national guidance. Nevertheless the Edinburgh model provides a possible way forward. By the early 1990s, 80% of women with type 1 diabetes booking at antenatal clinics had attended for formal pre-pregnancy counselling. This is an effective provision at population level, and led to a malformation rate of 1.5%. The time, effort and funding required to achieve such a goal should not be underestimated. One North American study demonstrated how the impact on anomaly rates and perinatal outcome of a specific project grant to provide pre-pregnancy and early pregnancy care was largely reversed following withdrawal of the ‘ring-fenced’ funds.

The difficulty is in implementing policies and engaging women in such care. Women not seeking pre-pregnancy care may be a selected, less motivated and less well-controlled group. Studies in the UK and the US have both shown that women seeking pre-pregnancy care are more likely to be married or in a stable relationship, to be non-smokers, to be employed, to be better educated, and to be more knowledgeable about diabetes, than those not seeking such care. There are virtually no data on the delivery of such care to women with type 2 diabetes. Recent authors have highlighted the particular difficulties in pre-pregnancy care provision to this heterogeneous group.

In Scotland, only 25% of women attended for formal pre-pregnancy care. This is reflected in the proportion of women with acceptable glycated haemoglobin at booking, with only 58% of women with recorded glycated haemoglobin values pre-pregnancy within acceptable limits. In the Dutch population study, where 75% of women had glycated haemoglobin values of less than 7%, 84% of pregnancies were said to be planned and 70% of women were taking pre-conception folic acid supplementation, they still had a malformation rate over three times the national rate. However, those who planned their pregnancy had a significantly lower malformation rate, though it was still above the national rate.

**Contraception**

Issues of contraception are frequently overlooked by adult diabetes services. There is no evidence that any particular contraceptive technique is ‘off limits’ for young diabetic women. Low-dose oestrogen preparations have minimal effect on diabetic control and there appears to be no effect on long-term diabetic complications, yet there is some evidence that young women with diabetes, if they are prescribed oral contraceptives, are more than twice as likely to be given a progesterone only preparation, than non-diabetic women. Progesterone only oral preparations can be used in established type 1 women provided there is close monitoring of both glycaemic control and lipid levels. There is no evidence that the risk of pelvic inflammatory disease is higher in type 1 diabetic women than in non-diabetic women. There are no data on long-acting progestagen preparations. Contraceptive advice to diabetic women needs to be both evidence and risk assessment based. Surveys in the US have shown similar sexual and
contraceptive behaviour in adolescent women with and without diabetes, with barrier methods being most common. Physician surveys in Germany and Greece suggest that barrier methods are advised largely because of uncertainty and a lack of national guidance on contraceptive issues.

High-risk groups

Particular groups of diabetic women may need specific pre-pregnancy advice. Women with retinopathy need to be aware that there is an increase in fetal growth restriction. Women with proliferative retinopathy should have therapy prior to pregnancy, as those with moderate to severe changes are at highest risk of further progression during pregnancy. They should be reassured that pregnancy will not affect long-term vision.

Women with nephropathy need to be aware that complications such as growth restriction, pre-eclampsia, and preterm delivery are increased. Danish data suggests a risk of 62% for prematurity and 42% for pre-eclampsia in those with microalbuminuria, and 90% and 64% respectively in those with frank proteinuria (more than 300 mg excretion per day). If women are receiving ACE inhibitors for existing hypertension or proteinuria then there should be discussion about altering therapy, as these drugs may have teratogenic and growth effects. There is evidence that intensive treatment with captopril from 4 to 6 months pre-pregnancy reduces the degree of proteinuria at the onset of pregnancy, even if discontinued at conception.

Care in pregnancy

Diabetic control

Women with both types 1 and 2 diabetes should be referred to a multidisciplinary service that includes obstetric and endocrine specialists, nurses and midwives with specialist expertise in diabetes and dietetic services. Only two-thirds of services in the UK provide such clinics. Of concern is that 11% of services had no specialist diabetes nurse.

Although most women will have substantial knowledge about diet and control, detailed advice will be needed to adjust for the nutritional demands of pregnancy. Ethnic issues need to be addressed at this early stage, and access to professional interpreting services is vital. There are particular difficulties in early pregnancy with nausea and vomiting which can have dramatic effects on diabetic control. Women need specific advice on how to manipulate this, and there should be early recourse to anti-emetic medication. Close and easy contact with specialist diabetic nurses in this period is vital to avoid rare instances of diabetic keto-acidosis secondary to hyperemesis. Partners and other close relatives should be involved. Glucagon should be available, with training on its use.

Insulin therapy usually involves multiple injection regimens, but this should not be proscriptive. Many younger diabetics are already on 3- or 4-injection systems. Women need to be aware that insulin demands will change rapidly. Even within the first trimester an initial rapid rise in requirements may be followed by a reduction of around 10%. Failure to appreciate the dynamics can lead to an increased risk of hypoglycaemia. Up to 70% of women report hypoglycaemic episodes in pregnancy, with one-third of these being severe, including the need for intravenous therapy, seizures or loss of consciousness. Many women lose the ability to detect ‘warning’ signs of impending hypoglycaemia, as a result of alterations in other hormone systems. Risk factors include duration of diabetes, rapid changes in insulin requirements and a history of severe hypoglycaemia. Women with type 2 diabetes being changed to insulin therapy need specific advice, as they are less likely to have suffered severe hypoglycaemic episodes.

As an outpatient, control is maintained by regular pre-prandial glucose estimations using hand-held home monitors. Modern home monitors store results, which is a useful quality control. Ideally, glucose testing should occur daily, but staff should be aware that this is not without complications. There have been reports of fingertip necrosis and sepsis in pregnancy. The degree of control is debated. There are data suggesting that early pregnancy control can influence the extent of both fetal macrosomia and adverse pregnancy outcome in its widest definition. Countering this is the risk of hypoglycaemia. The precise benefit from maintaining pre-prandial glucose levels at 3.5–4.5 mmol/l is...
not clear. There are few randomised trials and in these, very tight control, such as above, is associated with a massive increase in maternal hypoglycaemia without obvious perinatal benefit, compared with tight control being defined as values between 5.5 and 6.5 mmol/l.

More recently there has been a move towards postprandial monitoring, driven by observational studies suggesting reductions in macrosomia in particular. A small randomised study has confirmed that target values are more likely to be achieved using postprandial monitoring and that macrosomia, as measured by neonatal skin fold thickness, can be reduced. To date, studies are too small to determine if there are clinically important advantages to this type of surveillance.

Part of the emerging problem is that continuous glucose monitoring systems have shown that where measures of average control appear good, that this masks wide variation. Hyperglycaemia undetected by conventional monitoring occurs for around 3 h per day, and was present in 50% of samples in one study. Of more concern was the finding of undetected nocturnal hypoglycaemia in all subjects in the largest study. These swings in blood glucose using conventional therapy may account for the inability in general to demonstrate advantages to tighter control in the second and third trimesters.

If variation in blood glucose values throughout the day is clearly demonstrated to contribute to morbidity and mortality, then strategies to reduce this will need to be tested in robust clinical trials.

It has been shown that the intermittent use of continuous glucose monitoring may allow for better control and a reduction in the time spent either hyper or hypoglycaemic. Other strategies include increasing use of insulin analogues such as lispro. Studies suggest less variation in glucose values throughout the day, but to date, observational studies show no difference in any measured clinical outcome. Alternative methods such as functional insulin treatment, which allows patients much more flexibility in dosage and eating patterns compared with conventional care, has shown near normal outcomes, but there are no direct comparative studies. In a small randomised trial, the imaginative use of modern technology where home glucose monitors download nightly to a central computer and results are seen daily by specialist staff, has demonstrated marked reductions in the variation of blood glucose values but not in mean values, compared with normal monitoring. Few centres have sufficient experience with continuous subcutaneous infusion therapy to judge if this might reduce variation in glucose values, though in theory it is likely.

Women with type 2 diabetes should be converted to insulin therapy, although there are no randomised trials comparing outcomes from oral treatment versus insulin. Studies in insulin requiring gestational diabetes have shown no differences in clinical outcomes. Systematic review of the safety of oral agents in the first trimester has been unable to demonstrate an increased risk of fetal malformations. There are potential issues about neonatal hypoglycaemia and oral agents, especially if breast-feeding is preferred. Given such a data vacuum, clinicians should be wary of being too didactic in the face of maternal choice. Where insulin is used, then the target values are as for type 1.

At initial visits, assessment of retinopathy, nephropathy and neuropathy should be made. Most women with these complications will have already been identified. However, they represent a particularly high-risk group who will require more focused diabetic and obstetric care.

Rapid normalisation of blood glucose through a pregnancy regimen causes transient progression of retinopathy, although there may additionally be placental hormone factors, such as human placental lactogen and IGF-1, which contribute. The abruptness of the new control, and the extent of background retinopathy and duration of diabetes determine the extent and risk of this. The risk is greatest for those with existing proliferative retinopathy or who have co-existent hypertension, with almost half progressing to require treatment. Although one in six women without background retinopathy will develop signs of proliferative retinopathy during pregnancy, the risk should not be overstated. In one large mixed cohort study, only 2% required laser treatment during pregnancy. Retinal examination should be carried out at least once every trimester. Proliferative disease should be treated if found; photocoagulation is safe in pregnancy. Women should be reassured that there is good evidence that these problems will not contribute to long-term progression and that most changes regress in the postnatal period.

Diabetic nephropathy is felt to be due to primary glomerular injury secondary to hyperfiltration. Pregnancy increases GFR by 40–60%, and increased dietary protein needed in pregnancy increases filtration needs. The development of hypertension in pregnancy may challenge glomerular function. Despite these theoretical reasons why pregnancy should influence diabetic nephropathy, longitudinal studies have shown that where renal function is normal or mildly impaired, then pregnancy does not influence short- or long-term indices. This may be due to the improvement in GFR brought about by
improved glycaemic control, or by better blood pressure monitoring and treatment. Nevertheless, diabetic nephropathy increases the risks of fetal growth restriction, pre-eclampsia and preterm birth.

Women with nephropathy and significant renal impairment represent a difficult challenge. Blood pressure control is crucial, and combination therapy may be necessary. The progress of renal function and likelihood of pregnancy complications can to some extent be predicted from pre-pregnancy creatinine clearance rates and proteinuria. Where clearance is greater than 90 ml/min then problems are less common, and a normal increase in GFR in the first trimester is reassuring for both renal and perinatal outcome.

Urine for creatinine clearance and protein estimation should form part of the initial visit assessment. Blood pressure control should be tightened if necessary.

Antenatal care—first half of pregnancy

There has been persistent controversy regarding whether early pregnancy loss is more common in type 1 diabetes. There are experimental data examining cellular protective mechanisms in early embryogenesis that give theoretical credibility to an effect of hyperglycaemia on early fetal loss. Recent self-reported data from Denmark suggests that early miscarriage rates are 17.5% compared with 10–12% in the general population. Early miscarriage rates are difficult to assess, but most accept that the rate is in the order of 15% for type 1 diabetes. Mersey data over 10 years suggests a rate of 13%, and Scottish national data showed a rate of 14.7%.

There have been concerns over early embryo and fetal growth but detailed endocrine and ultrasound studies, which time ovulation and conception, have not demonstrated differences in early embryo length.

Accurate gestational dating by ultrasound is essential. Autosomal trisomy and neural tube screening is an integral part of maternity care. Diabetic pregnancies are not at increased risk from trisomy, but are at increased risk of neural tube defect. Poorly controlled diabetes alters HCG and AFP values, with the median levels of both being lower than the population average. These physiological alterations can be factored into risk calculations, though in practical terms there is no effect on trisomy 21 screening. The use of nuchal translucency measurements to screen for autosomal trisomy may avoid the need for complex adjustments and have the additional benefit of providing a marker for congenital heart disease.

The malformation rate in diabetic pregnancies remains high. Therefore detailed ultrasound examination is essential in this group. The timing of such scans, and who should perform them is uncertain. The common abnormalities are cardiovascular, neural tube, renal and skeletal anomalies. Many can be identified prior to the normal 20-week scan, and there is merit in considering detailed examination at 16 weeks for sacral agenesis and neural tube defects. Cardiac problems are the commonest abnormality in the Mersey data, with a rate of 3.2% and accounting for one-third of all anomalies. In the Dutch study almost half the major malformations were cardiovascular. Detailed examination of a regional malformation and diabetic database in the North of England has shown that great vessel abnormalities and tricuspid valve abnormalities are over represented compared with these malformations in the general population. This suggests that either detailed fetal echocardiography should be offered to all pregnant diabetic women or that, as a minimum, all should have a 5-chamber view at the routine screening scan.

Women with pre-existing vasculopathy, retinopathy and nephropathy are at increased risk of pre-eclampsia and growth restriction. The incidence of chronic hypertension is higher in women with type 2 diabetes. There is debate on the degree to which tight blood pressure control improves perinatal outcome, as there may be a trade off between reducing the risk of pre-eclampsia and the production of fetal growth restriction. There is less debate on the ideal levels of blood pressure where this is secondary to diabetes, and levels of 120–130 mmHg systolic and 70–80 mmHg diastolic are recommended.

Beta-blockers are best avoided, given their effects on glucose metabolism. Methylxophap or nifedipine tend to be the drugs of choice, and have a good safety profile.

Pre-eclampsia is common, affecting 12% of the Dutch cohort. Nearly 20% of the West Midlands cohort of type 2 diabetes developed either gestational hypertension or pre-eclampsia. Recent systematic reviews have suggested that low dose aspirin may reduce the risk of pre-eclampsia in high-risk pregnancies, but in the one trial that specifically examined its use in diabetes, no differences were found. Nevertheless, all diabetic women should be considered for this treatment following identification of a viable pregnancy. Therapy with the anti-oxidant vitamins C and E is currently being investigated in a randomised trial in the UK.
Regular growth scans are recommended. In the highest-risk group, with significant nephropathy or proliferative retinopathy, uteroplacental Doppler studies at 20 weeks may be helpful in planning later pregnancy care.

**Late pregnancy care**

The main issues in late pregnancy are the management of hypertension and pre-eclampsia, the prevention of macrosomia, fetal surveillance, and the timing and mode of delivery.

The management of developing hypertension in diabetic pregnancies is not different to that of other pregnancies complicated by hypertension. Drugs used and intervention levels are similar to those in early pregnancy. The importance of having baseline first trimester renal function and protein excretion documented cannot be overemphasised. It allows a clear distinction to be made in later pregnancy between worsening nephropathy and the evolution of pre-eclampsia. The appearance of new macro-albuminuria should always be assumed to be pre-eclampsia. The management issues for pre-eclampsia are no different from those in non-diabetic woman.

Where preterm delivery is necessary, corticosteroids should be given. Although short-term diabetic control is difficult, the benefits of survival and reduction in long-term disability for the infant make it unacceptable to withhold steroids. Increases in glucose levels usually arise 8–12 h after the first steroid injection and may warrant intravenous sliding scale therapy similar to that used in labour.

Prevention of macrosomia and its attendant risks of shoulder dystocia, difficult vaginal operative delivery, and Caesarean section for dystocia, is a key aim. Unfortunately there is no relationship between measures of average blood glucose control and birth weight, though intensive late pregnancy control may have an effect of up to 20%. Ultrasound growth differences between those infants destined to be macrosomic are evident by 18 week's gestation and appear independent of maternal weight. If there is correlation, then it is correlated with glucose control in the first half of pregnancy or pre-pregnancy. Diagnosis can be difficult. Most formulae for estimation of fetal weight perform poorly for large infants. Predictive values of ultrasound for macrosomia are around 60–70%. Serial ultrasound values need to allow for such error, and utilisation of some of the newer indices of longitudinal growth, such as the Z score of Owen and colleagues, could be valuable. Fetal abdominal circumference is the best single index, and has the added value of being the index best correlated with direct measures of fetal insulin. Examinations every 3–4 weeks are likely to be sufficient to yield data on macrosomia.

**Fetal surveillance**

Given the lack of knowledge on why infants of women with diabetes may die, the choice of monitoring is difficult. In recent overviews of fetal monitoring from both the UK and the US, the conclusion was that none of the current methods had any proven value in preventing poor outcome in diabetic pregnancy. Both emphasised how parameters could be influenced by maternal and presumably fetal glucose values. Both emphasised that false negative testing was commoner for all modalities in diabetic pregnancies compared with other high-risk pregnancies. Other groups have challenged the need and evidence for routine monitoring of diabetic pregnancies without hypertension or vasculopathy.

Where there is vasculopathy or hypertension, then clearly surveillance with uteroplacental Doppler will be important and valuable. However, studies have been unable to show any relationship between Doppler indices and any important outcome.

Most testing strategies rely on fetal heart rate monitoring. Interpretation must take into account alterations in fetal heart rate parameters in diabetic pregnancy. The baseline fetal heart rate rises, and there are fewer accelerations. Where computerised indices are used, time spent in high variability episodes is reduced, as are fetal movements and the frequency and magnitude of accelerations. False positive monitoring is common.

Given the high false positive rates of primary fetal heart rate monitoring, secondary tests of fetal biophysical function are frequently used. Care is again needed. There are alterations in fetal breathing rates, time spent breathing and the normal changes in response to changes in fetal behavioural states or uterine activity. Fetal movement rates are reduced, particularly gross body movements that form part of ultrasound biophysical scoring systems.

Despite this knowledge, weekly and indeed twice weekly monitoring schedules are commonly recommended. Some have a selective policy based on evidence of fetal hyperinsulinaemia, or maternal complications. Timing of commencement of monitoring is pragmatic. Most deaths occur after 32 weeks.
Timing and mode of delivery

Spontaneous preterm delivery rates of up to 25% have been reported. There is some evidence that this rate may be related to the degree of glycaemic control in the second trimester. Induced preterm delivery is common, and occurred in 20% of cases in the Dutch study. Not all had cogent clinical indications.

There is no evidence base to guide delivery timing. The balance is between late intrauterine death, the complications of preterm delivery and the risk of other obstetric interventions following induction. Most units practice delivery at 38–40 weeks gestation. The only trial of elective induction at 38 weeks in diabetes did not show any advantage. Similarly, a review of trials where induction for macrosomia has practiced has not demonstrated any reduction in perinatal morbidity over allowing spontaneous onset of labour.

Inductions of labour rates are high, 40% in the most recent analysis of Mersey data. Elective Caesarean section rates are also high, 38% in the Mersey region, and 24% in the Netherlands. Caesarean section in labour is common, being just over 40% in the Mersey regional survey, though much depends on the approach to labour. Even in a Dutch population, where background rates are traditionally low, the emergency Caesarean section rate was 20%. The Dublin group achieved emergency rates of less than 10%, though this was still higher than in non-diabetic labour.

Fourteen per cent of women achieving vaginal delivery in the Dutch study had shoulder dystocia. Nearly 30% of infants over the 90th centile for gestation had this complication. Despite the poor prediction of ultrasound, it does appear reasonable to consider elective Caesarean section where estimated weights are above 4.25 kg.

Peripartum care

Most use the intravenous route, with the capability to adjust both glucose and insulin rates. There is evidence that regular subcutaneous injection with soluble insulin may achieve similar control.

Women should follow their normal care until in established labour, particularly given modern thoughts on eating in labour. After this, intravenous dextrose should be delivered using a controlled device. If insulin is to be given intravenously then it should be given through a separate infusion.

There is a relationship between intrapartum glucose control and neonatal hypoglycaemia, independent of antenatal control. As a result, even in poorly controlled women, stringent intrapartum control may reduce or abolish this complication. The Newcastle group has carried out a series of investigations into the relationship between intrapartum control and neonatal hypoglycaemia. Where the maternal blood glucose can be kept at less than 8 mmol/l then neonatal hypoglycaemia is rare, whereas it is virtually universal if values are over 9 mmol/l. Given that this is one of the few properly audited regimens, and that a reduction in neonatal morbidity can be demonstrated, its use should be more widespread.

Following delivery, maternal blood glucose values fall rapidly. Some advocate stopping infusions immediately and returning to pre-pregnancy insulin. Others suggest a halving of the rate as an intermediate step. As Caesarean section is common, intravenous control may be required for 24 h, until near normal eating is established. The overall aim is to return the woman to her normal pattern of control as quickly as possible. If breast-feeding is being established, it must be appreciated that this requires calories, and diet and insulin may need to be adjusted.

The management of labour should not differ from normal. Someone from the medical or obstetric team should be contacted following admission. Given the risk of shoulder dystocia, experienced staff should be present at delivery. If there is doubt, assisted delivery should not be undertaken; there is no role for ‘trial of vaginal delivery’ in diabetic labour.

Conclusion

Over a decade ago the St. Vincent’s Declaration suggested that it should be possible to reduce the morbidity and mortality in diabetic pregnancy to near that of the normal population. Although individual centres continue to report such outcomes, in population studies in Europe this has not been achieved. There is evidence that strategies exist which might have an impact on pregnancy outcome, but that these may only be achieved by both re-organisation of care provision, and by women with diabetes becoming more actively involved in their care before pregnancy.

The rising tide of type 2 diabetes, even in largely Caucasian populations, means that this can no longer be regarded as an unusual disease in pregnancy. Data available show that outcomes are every bit as poor as those for type 1 diabetes, and particularly in Western societies there are significant social and cultural issues that need to be
addressed in order to deliver high quality coordinated services to this group.

New understandings in teratogenesis in general are beginning to disentangle why women with diabetes carry such a high-risk of major malformation. It is clear that this is not simply higher periconceptual glucose values. Both high and low glucose levels may have a role.

There is a new appreciation that the hour-by-hour variation in glucose values, even where control appears normal, may account for some of the difficulties in improving outcome. Clinicians are beginning to explore alternative methods of reducing this variation, but it is important that these are addressed in properly designed trials.

There is less doubt that better concentration on intrapartum insulin and glucose control can substantially reduce one of the major neonatal complications. This is an area traditionally left to the duty team, and is probably the least supervised aspect of diabetic care. Guidelines, available in 94% of UK units, are not a replacement for the specialist team.

The long-term outcome of children of diabetic mothers is a relatively unexplored area, but data suggest an impact on neurodevelopment, particularly coordination and attention.

Detailed guidance on changes in care patterns in the UK may need to await the results of the Confidential Enquiry into diabetes in pregnancy, not due to report until 2005 and 2006.

**Short case study**

You receive a letter from a local GP asking you to see a 32-year-old woman with type 1 diabetes. She has recently married, and, although the couple wish to consider pregnancy, they are afraid of the possible risks. She developed diabetes aged 7 years. The letter states that she has 2–3 admissions with severe hypoglycaemia every year, and has just had treatment for retinopathy.

What other information or results would you like to review before you see the couple?

How will you go about counselling in these circumstances?

You should arrange to contact her diabetes physician to obtain recent glycated haemoglobin results, and any details on her retinopathy, recent renal function and why she has such severe and frequent hypoglycaemia. Following this you should arrange either to refer her to the pregnancy diabetes team for assessment and discussion or to pre-pregnancy counselling services if they exist. If this is not possible an alternative would be to try and see one of the diabetes specialist nurses.

At this visit you should try to follow the guidance laid out by the American Diabetes Association in terms of assessment. This involves a full review of diabetes and complications, discussion of contraception, and discussion of risks of various outcomes dependent on her specific risk factors. It would be helpful to follow this up with a letter to the patient outlining the main points.

It will be important to be positive, particularly as you will need a good relationship for the pregnancy. They need to know the facts of the various risks of abnormality, pregnancy loss and complications, and it is important not to conceal these. However they can be reassured that pregnancy will not affect her diabetes long-term. You can emphasise that any pregnancy carries risk; it is simply that diabetes increase this. Even in type 1 diabetes, 75% of pregnancies are successful. You should take them through how good care before she becomes pregnant, including simple issues such as folate supplementation, can help to reduce these risks. You should finish by discussing contraception and timing, and by discussing how they think better diabetic control could be achieved.

**Practice points**

**Diabetic care**

- Early after transfer to adult services, women with diabetes should be reviewed with respect to pregnancy risks by a specific multidisciplinary team.
- Thereafter, consider discussion of contraception, pregnancy diabetic care and complications as part of annual visit to normal diabetic clinic.
- Develop and publicise access for formal pre-pregnancy clinic visits.
- At booking assess pre-pregnancy control and effects of early pregnancy nausea and vomiting.
- Ensure assessment of eyes, renal function and proteinuria.
- Review antihypertensive medication if relevant.
- Aim for tight control of preprandial glucose at 4.5–6.5 mmol/l as quickly as possible.
- Ensure organisation so that daily contact with the team is possible.
Early pregnancy obstetric care

- Viability scan.
- Caution in the adjustments used for serum screening, as it is dependent on glycaemic control.
- Assess for use of aspirin to prevent pre-eclampsia.
- Ultrasound at 16 weeks for neural tube defects and major skeletal abnormalities.
- Ultrasound at 20–22 weeks should include fetal echocardiography.

Late pregnancy care

- Uteroplacental Doppler at 24 weeks where risk of pre-eclampsia is high.
- Four-weekly growth scans; remember that the prediction of macrosomia by ultrasound is poor.
- Fetal monitoring from 32 weeks gestation if there is evidence of fetal hyperinsulinaemia, but not absolutely necessary if normal growth and good control.
- Use simple CTG monitoring but adjust for known physiological differences in interpretation.
- Consider delivery after 38 weeks.
- Mode of delivery decided on obstetric grounds.
- Discuss Caesarean section if estimated weight is likely to be over 4.2 kg.
- Intrapartum glucose control influences neonatal hypoglycaemia, so keep blood glucose less than 8 mmol/l.
- Choice of regime for intrapartum control, but ensure tight monitoring by ‘diabetic team’.
- Specialist staff immediately available at any vaginal delivery in view of high risk of shoulder dystocia.

Further reading

functional insulin treatment and modular outpatient educa-
in type 1 diabetes mellitus treated with insulin lispro.
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