Review Article

Management of diabetic pregnancy

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Introduction

The overall aim of the diabetic mother, her relatives and all members of the health care team is the safe delivery of a normal, healthy infant at term, preferably by vaginal delivery. This should be achieved with the minimum psychological and physical trauma, inconvenience and risk to the mother. Seen from another angle, avoidance of the many adverse pregnancy outcomes is the primary purpose of the intensified care offered to diabetic women undertaking pregnancy. These include spontaneous abortion and stillbirth, congenital malformation, macrosomia and biochemical disturbance in the neonate along with numerous aspects of maternal morbidity. Fortunately, most of these are wholly or partially ameliorated by optimal glycaemic control. The crucial aim of modern diabetes management in pregnancy is therefore normoglycaemia, though there are numerous other roles for the health care team. Gestational diabetes is covered separately, though many of the issues are as relevant as they are to 'pre-gestational' diabetes. There is enormous laboratory research interest in the area of diabetes and pregnancy, but most of our knowledge about practical management comes from clinical and epidemiological studies which are therefore the main focus of this review.

Management of established diabetes

The team approach

Organization of a multidisciplinary health care team is crucial to the eventual outcome in diabetic pregnancy.¹ However, we should not forget how little can be achieved without the help of the

patient. Ideally, obstetrician, diabetologist, diabetes specialist nurse, midwife and dietician should all be represented in a combined clinic, but where local facilities do not permit, at least ready access to all these services at frequent intervals is essential. A neonatal paediatrician should also be involved, though not necessarily in the clinic, in relation to decisions affecting subsequent neonatal care. As a part of these organizational arrangements, clear lines of communication must be established with the patient's general practitioner and the community services. The increasing use of patient-held notes which can be used by all disciplines is an effective way of achieving this.

Patient education

Ideally, patient education or re-education should begin before conception and can usefully involve the husband/partner and other family members as well. The areas to be covered must include sick day rules, blood glucose monitoring technique, testing for ketonuria, review of diet and exercise, and the application of precise blood glucose targets. Injection of glucagon by the partner is a useful technique which may allow the home management of episodes of severe hypoglycaemia. The aim should be that the patient will have the education and confidence to make the majority of therapeutic decisions herself. Clearly, this is an area where the dietician and diabetes specialist nurses have a major role. Such matters may be discussed years before pregnancy is planned but concentration of resources to a pre-pregnancy clinic is probably the most effective method of delivering the necessary care.

Pre-pregnancy glycaemic control

The value of pre-pregnancy clinics in improving outcome is now so well established^{2,3} that the principle has been adopted successfully on a state-wide basis in some American centres.^{4,5} Some congenital malformations, particularly the caudal

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regression syndrome are very much more common in the offspring of diabetic women compared to non-diabetic women.⁶⁻⁸ The reduced incidence of malformations in women with good control at pregnancy diagnosis implies a major teratogenic role for hyperglycaemia.⁹ Indeed in this series, the incidence of congenital malformation was reduced to that of the non-diabetic population by careful biochemical control before conception. Since pregnancy is usually not diagnosed until 3-4 weeks after conception, a crucial period of embryogenesis may be affected unless pregnancies are planned and glycaemic control optimized beforehand. Most studies have failed to identify a threshold level of glycaemic control at which the incidence of malformations rises.⁸ The target should therefore be a glycosylated haemoglobin value within the normal range at the time of conception as well as normal pre- and post-prandial sugars. The enhanced risk of hypoglycaemia associated with good biochemical control should not be forgotten.¹⁰

The incidence of spontaneous abortion in diabetic pregnancy has also been shown to be related to poor glycaemic control in the first trimester.^{11,12} The precise mechanism by which hyperglycaemia increases the risk of abortion is unclear, but again there appears to be no clear safe threshold value of glycosylated haemoglobin which confers protection from first trimester miscarriage.⁸ This further argues for establishing normoglycaemia before conception.

Glycaemic control during established pregnancy

Home blood glucose monitoring has revolutionized the achievement and maintenance of normoglycaemia. Urine testing as a means of monitoring glycaemic control in pregnancy is not satisfactory, primarily because of the fall in renal threshold during pregnancy. Capillary blood glucose should be measured by the patient before and 90-120 minutes after each meal, and also at bedtime. It is useful to measure blood glucose occasionally at night (3-5 am), to detect undertreatment or asymptomatic hypoglycaemia. It is unnecessary to perform a seven-point profile every day when stable, but this should be undertaken at least twice weekly, and more often when insulin requirements are increasing rapidly in the second half of pregnancy.

Targets for pre-prandial capillary blood glucose should be between 3.0 and 5.0 mmol/l, with post-prandial values about 2.0 mmol/l higher. The degree of accuracy required means that a personal blood glucose meter is essential. These are now inexpensive (around £30) but most centres can offer to loan a meter to the mother for the duration of the pregnancy. A number of meters are now available which incorporate a memory, providing useful

reassurance against falsification of recordings in appropriate patients. Some meters also have the facility for direct downloading of the memory to a desktop computer.

Most emphasis has normally been placed on pre-prandial blood glucose recordings but there is increasing evidence that post-prandial values^{13,14} and possibly blood glucose variability¹⁵ are important in the determination of pregnancy outcome. In the study reported by Jovanovic-Peterson and colleagues,¹³ third trimester non-fasting blood glucose values were a better predictor of percentile birth weight than fasting blood glucose values. Overall glycaemic control can also be assessed using glycosylated haemoglobin or fructosamine. Both measures remain reliable for an individual patient during pregnancy but serve mainly as reassurance, since the values obtained are historical rather than current. However, it is appropriate to measure one of these parameters at 2-4 weekly intervals.

Hypoglycaemia

Insulin sensitivity falls as pregnancy progresses, particularly during the third trimester, leading to a gradual increase in insulin dose. The fall in insulin sensitivity gives some protection against hypoglycaemia, but this complication may be troublesome in the first half of pregnancy, particularly when hyperemesis complicates the picture. In a study of 189 pregnant diabetic women, Drury¹⁶ found 230 episodes of significant hypoglycaemia (requiring help from another person) which were actually most common in the second trimester. Hypoglycaemia was common in the night, a fact of which patients, spouses and relatives must be made aware. This is of particular concern for the pregnant diabetic woman who lives alone, in whom glycaemic targets may have to be relaxed. Hypoglycaemia at night usually responds to delaying the administration of all or part of the evening long-acting insulin until bedtime, consequently delaying its peak of activity. In pregnancy, hypoglycaemia while driving is another area of concern but unfortunately there is little objective information. However, because of the greater risk of hypoglycaemia with tight biochemical control, it is prudent to recommend as little driving as possible, with careful attention to meal timing and measurement of blood glucose before driving.

There have been concerns, particularly from animal studies, that hypoglycaemia might also be teratogenic or in another way harmful to the fetus.^{17,18} However, the duration of hypoglycaemia in these studies and its timing in relation to organogenesis are difficult to equate with the human situation. Reassuringly, in the Diabetes in Early Pregnancy Study in the United States, no

relationship was shown between episodes of hypoglycaemia in the first trimester and subsequent malformations in 626 diabetic women studied.¹⁹ Drury¹⁶ reports that the perinatal loss rate was 5.3% of 75 pregnancies complicated by significant hypoglycaemia and 7% in 114 patients who reported no hypoglycaemia at any stage of pregnancy, providing additional reassurance about the low risk of hypoglycaemia to the fetus in the clinical situation. Patient recall of hypoglycaemic episodes may be short and many asymptomatic episodes may go undetected, although the careful diary-keeping in the study of Mills *et al.*¹⁹ should have overcome this difficulty.

For practical purposes, occasional hypoglycaemia is a much lower risk to the fetus than persistent hyperglycaemia. However, it remains important to reduce to an absolute minimum any episodes of severe or asymptomatic hypoglycaemia which might compromise driving, performance at work and care of young children.

Hyperglycaemia and ketoacidosis

Patient self-monitoring has allowed early detection of severe hyperglycaemia. This is usually due to intercurrent viral or urinary tract infection. In pregnancy, early action is essential to prevent progression to ketoacidosis, because of the altered fuel metabolism and increased tendency to ketogenesis.²⁰ The application of sick day rules in the event of hyperglycaemia, which must include urine testing for ketones^{21,22} should allow early intervention. Immediate advice must be available in person or by telephone, to control the metabolic derangement with additional doses of soluble insulin and oral fluid and carbohydrate. Where vomiting precludes the latter, immediate admission is mandatory. Where home management has failed to produce improvement after 6 hours, admission for intravenous treatment is essential, since ketoacidosis may develop rapidly in the pregnant patient.

Ketoacidosis is a serious risk to mother and fetus, with the older literature giving a fetal loss rate of 30% for ketoacidosis, rising to 64% when maternal coma was also present.²³ A study of 20 cases of ketoacidosis occurring between 1972 and 1987 in 560 diabetic pregnancies found a fetal loss rate of 35%.²⁴ There were no maternal deaths. However, all of the fetal deaths had occurred by the time of admission. Factors which appeared to predict fetal death included more advanced gestation and higher plasma osmolality, urea and glucose at admission. The main implication of this series is the importance of patient education and prevention. Alertness to symptoms of diabetes must be maintained by all health care workers

involved with pregnant women, as six out of the 20 patients were newly presenting insulin-dependent diabetics and the accounted for four of the seven fetal deaths.

Diet

In pregnancy, more care with dietary prescriptions is necessary to allow predictable and smooth glycaemic control. The increased tendency to ketogenesis²⁰ makes between-meal snacks of greater importance. Most women eat a little more in pregnancy, although weight gain may be achieved at the expense of a reduction in energy expenditure.^{25,26} Additional calorie requirement should normally be in the form of complex carbohydrate, but protein supplementation may also be required where renal losses are high. A comparison of diet in pregnant and non-pregnant diabetic women suggested that achieving the ideal diet may be difficult²⁷ and a pragmatic approach with emphasis given to appropriate alteration in insulin regime may be more important.

Insulin

The variation in insulin regimes required to offset the increased risk of hypoglycaemia and the increased insulin requirement of later pregnancy have been discussed above. These changes require constant review of home monitoring records and measures of overall glycaemic control. A change to separate soluble and medium- or long-acting insulins may be necessary, since they allow greater flexibility than 'fixed mixtures'. Insulin infusion pumps are not generally recommended in pregnancy because of the higher than usual risk of ketoacidosis²² and the exceptional motivation required from the patient with currently available technology.^{22,28,29} The technique is undoubtedly useful in some situations but because of the need for expert support at all times, it cannot be recommended to the majority of district hospital services.

There has been concern about the influence of insulin species on the genesis of neonatal hypoglycaemia and macrosomia.^{30,31} In one study of infants of mothers treated with animal insulin, bovine or porcine insulin was found to account for 27% of cord serum insulin concentration at birth.³² The concentration of animal insulin in cord serum correlated with birthweight and the concentration of anti-insulin antibodies in both mother and fetus. The authors suggest as have others previously, that animal insulin may be transferred to the fetus as an insulin-antibody complex, where it contributes to hyperinsulinaemia and macrosomia. In this study, there was no relationship between maternal blood

glucose control assessed by glycosylated haemoglobin and fetal macrosomia.

However, in a more recent study³³ human and animal insulins were administered in a randomized fashion from before 20 weeks of pregnancy. Human insulin was found to provide superior glycaemic control with a lower incidence of macrosomia and no evidence that trans-placental passage of animal insulin or antibodies was responsible for the poorer outcome in the patients treated with bovine or porcine insulins. Interestingly, C-peptide levels were still lower at 3 months in the infants who were exposed to human insulin in later pregnancy. It is therefore appropriate to recommend the use of human rather than animal species insulin in pregnancy, preferably making the change in the pre-pregnancy clinic. Most young women with diabetes have probably now been treated with human insulin from diagnosis, since its introduction to the UK in 1985. Concerns about the increased risk of hypoglycaemia in human insulin treated patients are fortunately beginning to lessen,³⁴ although the precise reasons for the clinical phenomenon have not been fully resolved.

Oral hypoglycaemic agents

Non-insulin-dependent diabetes (NIDDM) is less common in the age group likely to undergo pregnancy. Patients who possess the clinical characteristics of NIDDM may have been treated with oral hypoglycaemic agents before pregnancy. Few would now commence oral hypoglycaemic agents in pregnancy, although this has been shown to be a valuable therapeutic manoeuvre in socially deprived patients in South Africa.^{35,36} In these studies, a perinatal mortality rate in diabetic pregnancy of up to 35% was reduced to 7% using oral agents only and the difficulties of administering insulin with limited support in a predominantly rural setting were highlighted. In the United Kingdom however, neither metformin nor sulphonylureas should be used in pregnancy. There is no direct evidence of teratogenicity³⁷ but metformin may be associated with growth retardation, and trans-placental transfer of sulphonylureas promotes hyperinsulinaemia and macrosomia in the fetus despite good glycaemic control in the mother, putting the infant at increased risk of hypoglycaemia during the first few days of life. Therefore, it is preferable to transfer women from oral agents to insulin in the pre-pregnancy clinic or certainly in the early stages of pregnancy.

Complications of diabetes in pregnancy

It is essential to be aware of any complications of diabetes at the outset of pregnancy. This fact was

recognized many years ago when White's classification was first published, but our current understanding of the aetiology of adverse outcomes in mother and fetus makes this classification largely obsolete. Screening for complications by clinical and biochemical examination at a pre-pregnancy or booking visit is essential. For those without complications at the outset, it is unusual for new problems to arise, but progression of established complications during pregnancy is well recognized. Those women with either retinopathy or nephropathy represent a minority of diabetic women in pregnancy but they do require intensive follow-up to detect deterioration at an early stage.

Neuropathy

Peripheral neuropathy of the glove and stocking type causes few specific problems in pregnancy. Established neuropathic ulceration or joint disease is uncommon in this age group, but if problems arise, appropriate combined management between physician and chiropodist should allow a good outcome. Entrapment neuropathy is more likely to be a problem in diabetic pregnancy, particularly the carpal tunnel syndrome. However, since the syndrome is more common in pregnancy, symptomatic treatment and splinting are all that are likely to be required, with resolution to be expected after delivery.

Where the pregnant diabetic patient has advanced complications, these may include autonomic neuropathy.³⁸ The presence of abnormal cardiovascular autonomic function tests has been shown to predict adverse pregnancy outcome.³⁹ Clinically, visceral autonomic neuropathy is the main difficulty, particularly gastropathy. Diagnosis in pregnancy may be difficult because of the known reduction in gut motility and the contraindication to established radiological diagnostic tests. The greatest risk to mother and fetus is ketogenesis secondary to protracted vomiting. Long periods in hospital for intravenous therapy may be needed, with long-term management including small, frequent meals and combinations of drugs to both enhance gut motility and reduce central sensation of nausea. Macleod *et al.*³⁸ advises giving early consideration to total parenteral nutrition in refractory cases.

Retinopathy

Regular fundoscopy in pregnancy aims to detect sight-threatening deterioration. The most likely event is progression from background change to pre-proliferative and proliferative change with subsequent vitreous haemorrhage. Fortunately, the majority of such haemorrhages clear spontaneously, and treatment of established and

recently developed neovascularization during pregnancy with laser photocoagulation is without hazard to the fetus. The subject has been reviewed in detail, with clear advice given regarding counseling and management of retinopathy both before and during pregnancy.^{40,41} The current difficulty is to reconcile the interests of the mother and the fetus when it is apparent that retinopathy may deteriorate when there is a rapid improvement in glycaemic control as in early pregnancy.⁴² However, a larger study comparing pregnant and non-pregnant diabetic patients suggests that pregnancy itself is independently associated with deterioration in retinopathy (relative risk 2.3) despite improved control in both groups.⁴³ It is therefore necessary to accept the increased ophthalmological morbidity as a consequence of pregnancy and to maintain a high level of awareness whilst striving for normoglycaemia. Klein and colleagues⁴³ also demonstrated that initial glycosylated haemoglobin concentration and blood pressure independently predicted progression of retinopathy, emphasizing the need for multifactorial risk assessment.

Nephropathy

In the presence of renal disease in the diabetic patient, pregnancy is accompanied by an increased incidence of hypertension, premature delivery and perinatal mortality. In these circumstances, pregnancy is not to be undertaken lightly. Hare⁴⁰ suggests that a successful pregnancy is unlikely with a serum creatinine greater than 300 $\mu\text{mol/l}$. In the non-pregnant diabetic, renal disease usually progresses over a considerable period of time from microalbuminuria to nephropathy with easily detectable proteinuria and subsequently to established renal impairment. This progression can be slowed by tight glycaemic control,¹⁰ dietary protein restriction and the use of angiotensin converting enzyme (ACE) inhibitors. Apart from improved glycaemic control, these measures are impractical in pregnancy and dangerous in the case of ACE inhibitors which cause fetal renal failure and oligohydramnios.⁴⁴ Experience with renal failure in pregnancy^{45,46} indicates that pregnancy *per se* does not have a permanent deleterious effect on renal function. However, hypertension and proteinuria are exacerbated. Monitoring of renal function using 24 hour collections for protein excretion and creatinine clearance is essential.

It has been suggested that microalbuminuria may be an early marker of renal difficulties in diabetic pregnancy.⁴⁶ However, an acceleration of the disease process is usually used as an indication for delivery, as the distinction between the gradual worsening of proteinuria and blood pressure, and the development of eclampsia is unclear. Treatment with well-established anti-hypertensives in-

cluding hydralazine, methyldopa, beta blockers and calcium channel antagonists is the rule, with hospitalization and bed rest where necessary. Relative hypovolaemia in this situation, as with non-diabetic pregnancy-induced hypertension contraindicates the use of diuretic agents, except where pulmonary oedema threatens the mother.^{47,48}

Pregnancy-induced hypertension in the absence of pre-existing renal disease deserves special mention because of its greatly increased incidence in diabetic pregnancy. In a study of 334 diabetic pregnancies, the incidence of pre-eclampsia was 9.9% compared to only 4.3% in non-diabetic controls.⁴⁹ Pre-eclampsia is also more common in patients with gestational diabetes, although the reason for the increased incidence in both gestational and pre-gestational diabetes remains enigmatic. The risk of pre-eclampsia can be reduced by tight glycaemic control, despite the hyperinsulinaemia which this invariably entails.⁵⁰ The perinatal mortality is greatly increased from 0.3% to 6.0% when pre-eclampsia complicates diabetic pregnancy but much of this is accounted for by the need for premature delivery in these patients.⁴⁹

Management in labour and the puerperium

There are many different regimens for the metabolic management of diabetes in labour and the immediate puerperium. Nowadays, all rely on the combination of intravenous insulin infusion, most conveniently delivered by syringe pump, and intravenous dextrose given with potassium supplementation. The essential points are to ensure euglycaemia during the second stage of labour to reduce the risk of neonatal hypoglycaemia, whilst tailoring the insulin and carbohydrate dose to suit the patient. Local preferences will dictate the details but a few points are worthy of note. Regular (at least hourly) blood glucose monitoring is essential. The frequency of testing may have to be increased as the second stage ensues, since the physical effort may increase caloric requirements and precipitate hypoglycaemia. Following the delivery of the fetus and the placenta, insulin requirements fall and again maternal hypoglycaemia may be a problem if the insulin infusion rate is not reduced at this stage.

It is conventional to resume the pre-pregnancy daily dose of insulin immediately after delivery. In women who plan to breast feed, additional dietary carbohydrate is required and a further reduction in insulin dose may be necessary. All women should be encouraged to breast feed for as long as is practicable and diabetic women are no exception. However, it is an additional distraction to carbohydrate metabolism and requires extra support from health care staff. Disappointingly, fewer

diabetic than non-diabetic women continued to breast feed one month after delivery in a study of endocrine disorders and lactation.⁵¹ The diabetic women in this study also had a reduced milk volume compared to controls, which may account for this difference. It is possible that this again reflects a higher incidence of pre-term delivery.

Contraception is an issue which is often discussed at the post-natal visit. Women with diabetes deserve special attention in this regard because of the need to plan pregnancy carefully. It is usual for glycaemic control to relax a little after pregnancy for a number of reasons, with obvious implications for unplanned pregnancy. Most contraceptive methods are suitable for the diabetic patient in the short term. The main issue is to reduce the burden of excess lipid and vascular risk which may be attached to currently available oral contraceptives and to avoid agents with deleterious effects on insulin sensitivity.⁵² For this reason, a sterilization procedure should be considered as soon as the family is complete.

Gestational diabetes

Glucose tolerance may deteriorate in pregnancy as insulin resistance increases.⁵³ The majority of cases of impaired glucose tolerance diagnosed in pregnancy represent patients who will return to normal glucose tolerance after delivery. Glucose intolerance is usually mild without clinical manifestation but may still be associated with significant maternal-fetal complications. Most clinicians therefore advocate some form of screening. There has been considerable controversy recently regarding the correct method and timing of screening for impaired glucose tolerance and indeed doubt about whether screening is necessary at all.⁵⁴⁻⁵⁷

There is also disagreement about the correct criteria for diagnosing the condition, but however defined, it is certainly not without increased morbidity for both mother and infant which rises with increasing glucose intolerance. An incidence of non-insulin-dependent diabetes mellitus (NIDDM) of up to 65% at 25 years⁵⁸ has been reported in women followed up after the detection of abnormal glucose tolerance in pregnancy. Ongoing dietary treatment and advice after the index pregnancy reduced the incidence of subsequent NIDDM to 6.4% at a mean of 12.9 years in another study, suggesting benefit from intervention in the long term.⁵⁹

The evidence that treatment of gestational diabetes reduces maternal morbidity during the pregnancy is less clear.⁵⁴ There is evidence of an increased operative delivery rate and higher incidence of hypertensive complications in gestational diabetic pregnancy but these may not be altered by

treatment. From the point of view of the fetus, gestational diabetes clearly increased perinatal mortality rates in early (and ethically unrepeatable) studies.^{60,61} The effect of insulin treatment on outcome is harder to assess.^{54,62} There are many other factors which have reduced overall perinatal mortality in the last 30 years, particularly the development of neonatal intensive care. Only a very large study would now have sufficient statistical power to confirm that treatment of gestational diabetes was the only reason for the improvement in perinatal mortality observed in these early studies.

Screening for gestational diabetes

Two reviews^{54,57} conclude that the only indication for treatment of gestational diabetes and thus the only justification for screening is the prevention of macrosomia. However, macrosomia is often ill-defined and may take no account of gestational age or race.⁶³ Furthermore, fetal weight has many determinants other than hyperglycaemia, including maternal height, weight, age⁶⁴ and possibly genetic factors determined by both parents.^{65,66} Even in diabetic pregnancy, the relative risk of macrosomia attributable to a maternal weight above 80 kg is greater than that due to a mean blood glucose >7.2 mmol/l in the third trimester.⁶⁴ Sadly, the obese gestational diabetic is more likely to have a large infant and less likely to benefit from insulin treatment than her lean counterpart.⁶⁷

Another criticism of studies which have failed to show a benefit from screening and treatment is that these interventions have come too late to influence outcome.⁵⁶ Recent data support the possibility that maternal diabetes in the second trimester may influence fetal pancreatic growth, with consequences for the development of diabetes in later life in the offspring.⁶⁸ Confusingly, fetal undernutrition as evidenced by low birth weight has also been linked with NIDDM in later life.⁶⁹ Evidence of reduced intelligence in offspring of diabetic mothers also argues for extension of screening programmes for gestational diabetes into the second trimester.⁷⁰ There may be other reasons to screen for and treat gestational diabetes,⁷¹ not least the realization that the intensive antenatal care may be targeted at a disadvantaged population.⁵⁵

How then should screening for gestational diabetes be undertaken and at what stage of pregnancy? Urine testing for glucose is the time-honoured method but lacks specificity in later pregnancy because of the fall in renal threshold. However, it is much more specific in the first trimester and is a valuable method for detecting undiagnosed NIDDM and IDDM patients.⁷²

In the USA, the recommended method is universal screening with a 50 g oral glucose challenge at

booking in the first trimester, followed by a 100 g, 3 hour oral glucose tolerance test (GTT) if appropriate.⁷³ However, this invasive approach is not without problems including cost, poor reproducibility and a high incidence of vomiting. Furthermore, the definition of an abnormal result is based on the risk of later NIDDM in the mother, rather than fetal morbidity in the index pregnancy.⁵⁵ Studies of physicians practices indicate that this policy is adopted by 47–96% of doctors, depending on their training background.^{74,75} No such data for screening practices are available for the UK where the 100 g GTT has never been adopted.

Glucose tolerance alters with pregnancy, such that 2 s.d. above the mean of the 2 hour value after a 75 g load is 7.5 mmol/l at 14–20 weeks and 9.6 mmol/l at 28–37 weeks in a highly selected young, non-diabetic, UK population.⁷⁶ If this test is to be used, timing is therefore crucial. The Diabetic Pregnancy Study Group of the European Association for the Study of Diabetes (EASD) recommends screening at 28 weeks using the 75 g oral GTT with appropriate adjustment of normal ranges.⁷⁷ The 2 hour value adopted for diagnosis in venous plasma using a specific glucose oxidase method was 9.0 mmol/l (that is, 2 s.d. above the mean) rather than the non-pregnant value of 8.0 mmol/l. In this much larger international study, there were no differences between glucose tolerance in the second and third trimesters, but women in the first trimester (<117 days) had considerably better glucose tolerance (mean + 2 s.d. value of 6.8 mmol/l). Ethnic differences in the incidence of gestational diabetes have also been reported,^{78,79} with up to 15% in Asian patients. This reflects differences in the background incidence of NIDDM between different populations and thus it is probably appropriate to retain one normal range for all races, although there are no satisfactory outcome data to support this view.

Glucose tolerance as defined by a GTT is a continuum in most populations, without a bimodal distribution.⁸⁰ The separate use of the terms gestational glucose intolerance and gestational diabetes may be irrelevant in pregnancy, since the latter is derived from non-pregnant populations and indicates a later risk of microvascular complications which are exceptionally rare in GDM. A 2 hour value in the 75 g GTT of 9.0 mmol/l or less was not associated with adverse outcome in either mother or infant in the EASD study reported by Lind and Phillips.⁷⁷ Therefore, all pregnant women with a 2 hour glucose value after 75 g load exceeding 9.0 mmol/l should be considered at increased risk along with their infants, until we have evidence to the contrary.

Screening using a random, non-fasting blood glucose has now been advocated in many cen-

tres^{81–83} and represents a useful compromise between the low specificity of urine testing and the major implications of universal GTTs. Reflectance meters have been used but probably lack the necessary accuracy because of difficulties with sampling, multiple operators and inadequate quality control in most centres. Unfortunately, most studies have examined the accuracy of sampling at the start of the third trimester, on the assumption that this is the only time when intervention is appropriate. The correlation between the detection of gestational diabetes in early and later pregnancy using a random blood glucose measurement is poor.^{83,84} However, screening at booking is worthwhile to detect undiagnosed IDDM and NIDDM.⁸⁵ In the largest published study of over 12,000 patients in India,⁸⁶ this proved to be a useful method of selecting patients for further investigation with a GTT. However, the time of booking was not given. Conventional risk factors for gestational diabetes including obesity, previous gestational diabetes, previous macrosomia and family history of diabetes were shown to be poor predictors of impaired glucose tolerance. Indeed 42% of patients with a final diagnosis of gestational diabetes would not be detected using conventional risk factors alone as an indication for a GTT. This is in accord with other authors^{61,81–83} in Europe and the USA.

The conclusion from studies using a universal random glucose estimation at 28–30 weeks is that a locally derived normal range and its upper 95th centile should form the basis of the indication for selecting patients for a formal GTT. However, women with multiple conventional risk factors for macrosomia or gestational diabetes but a normal random blood glucose should also undergo oral glucose tolerance testing because of the occasional false negative in some of these studies. The low cost of a random blood glucose measurement will allow measurement to be undertaken more than once during pregnancy.

Management of gestational diabetes

Having detected abnormal glucose tolerance, if counselling has not been a part of the screening programme, the implications of the diagnosis must now be explained to the mother. Dietary treatment is the initial approach with restriction of refined carbohydrate. Teaching the patient to self-monitor blood glucose levels is essential as the results of these will determine whether the patient requires insulin treatment. Upper limb aerobic exercise has also been shown to be a safe and effective adjunct in the management of gestational diabetes, reducing the number of patients who go on to require insulin treatment.^{87,88}

Targets based on fasting venous plasma glucose > 5.3 mmol/l have been shown to be associated with increased risk of large for gestational age infants.^{89,90} However, the American Diabetes Association recommends insulin treatment when fasting venous plasma glucose values above 5.8 mmol/l or post-prandial values > 6.7 mmol/l are obtained.⁷³ Such specimens are impractical for day to day use and a pragmatic approach using home capillary glucose monitoring with or without a meter is more appropriate in this country. These are roughly equivalent to venous plasma values and insulin treatment should be considered when fasting values consistently exceed 5 mmol/l and post-prandial values are consistently above 7 mmol/l. The choice of insulin treatment is usually straightforward with twice daily isophane insulin initially. Soluble insulin may be added if post-prandial peaks remain uncontrolled. Large doses of insulin may be required as the pregnancy approaches term but the risk of hypoglycaemia in these patients is low because of the marked insulin resistance.

The management of delivery in an insulin-requiring gestational diabetic differs little from that of the pre-gestational diabetic. It is conventional to discontinue insulin immediately after delivery and monitor blood glucose for 24 hours. Persistent hyperglycaemia strongly suggests that the patient has true diabetes diagnosed incidentally during

pregnancy, rather than impaired glucose tolerance as a consequence of the insulin resistance of pregnancy. Insulin treatment during delivery is not required for those women who did not require insulin during the pregnancy. It is important to be aware that dextrose containing intravenous fluid in these women may precipitate hyperglycaemia, with the attendant risk of hypoglycaemia in the infant immediately after birth. In all patients who have shown impaired glucose tolerance during pregnancy, a repeat GTT should be organized 4–8 weeks after delivery and interpreted according to guidelines for non-pregnant patients.

Approaches to treatment of gestational diabetes are currently fairly well defined, aiming for normoglycaemia as in pre-gestational diabetes. There is still controversy about the correct approach to screening which cannot be resolved on the basis of historical literature.⁹¹ Whilst awaiting answers from prospective studies, a pragmatic approach to screening using inexpensive methods which are acceptable to patients should therefore continue until appropriate action is clearer.

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