DIABETES MELLITUS

Afolabi BB, Abudu OO.

DEFINITION

Diabetes mellitus is the metabolic disease that results from lack of insulin.
The World Health Organisation Expert Committee on diabetes mellitus defined the disease in terms of blood glucose levels. If the random blood glucose is equal to or greater than 11.0 mmol/l in a (non-pregnant) patient with polyuria, polydipsia, weight loss and occasional glycosuria, that patient has diabetes.

If a patient without the above symptoms and signs has a fasting glucose value greater than 8.0 mmol/1, and/or the 2 hour glucose level following a 75g oral glucose load (OGTT) is greater than 11 mmol/1, the patient is diabetic. Any patient whose random blood sugar is less than 8.0 mmol/l or fasting level is less than 6.0 mmol/1 does not have diabetes mellitus.

A diagnosis of impaired glucose tolerance (IGT) is made if the fasting level is less than 8.0 mmol/1 but the concentration 2 hours after an oral glucose load of 75g is between 8.0 and 10.9 mmol/l.

The WHO committee also recommended that the same definition for non-pregnant women be applied in pregnancy so as to achieve international standardisation. However, it is known that the fasting and the random blood glucose levels in pregnant women are significantly lower than in non-pregnant women.

CLASSIFICATION

There are three broad categories found in pregnancy:

(1) Established diabetes mellitus - women who were already diabetic before pregnancy and are being managed on diet,insulin or oral hypoglycaemic agents.
(2) Gestational diabetes mellitus - women in whom diabetes commences or is recognised for the first time during pregnancy. A small proportion of such women may have had occult diabetes before pregnancy.
(3) Impaired glucose tolerance – women whose blood glucose levels correspond to the values shown above.

INCIDENCE

The incidence of diabetes in pregnancy in any obstetric population will vary according to whether diabetic screening is done routinely or not in that population. In a Lagos University Teaching Hospital study, a prevalence rate of about 15 undiagnosed diabetic women per 1,000 antenatal population has been reported. Generally the incidence of diabetes in pregnancy is between 0.25 and 2.5 per cent and could be higher in highly specialised units that take diabetic referrals.

Screening for *gestational diabetes* is a controversial issue. Certain risk factors have traditionally been used to define "potential diabetics". These factors include a history of unexplained stillbirths, history of having had macrosomic babies (> 4kg), family history of diabetes in a first degree relative, and/or

the presence of glycosuria in the current pregnancy. Using these criteria alone about as many as 60 per cent of diabetic patients and those with IGT would be missed, and a lot of non-diabetics would be included as there are many other causes of these clinical factors than impaired glucose tolerance. An example is glycosuria which is commonly seen in pregnancy because of the reduced renal threshold for glucose. Very few pregnant women with glycosuria would be found to have diabetes after an OGTT. However, screening all pregnant women would be even less sensitive and specific, and very expensive. Hence "clinical risk factor" screening is still used in many units, testing the women with the above features using blood glucose levels. The definition of diabetes is then based on WHO recommendations, using the OGTT as described above. Screening may be done initially at booking and then repeated at about 28 weeks gestation when the detection rate is higher and there is still a chance to treat the woman and improve outcome.

PATHOPHYSIOLOGY

Table 13.1 summarises the metabolic effects of insulin. The absolute or relative lack of insulin results in hyperglycaemia, protein catabolism, lipolysis and ketogenesis. These metabolic effects of lack of insulin lead to the major findings in diabetic ketoacidosis. In pregnancy, significant changes in carbohydrate and fat metabolism occur which increase the tendency for development of ketoacidosis in the diabetic.

Target organ	Metabolic effect of insulin
A. Liver	Inhibition of glyconeogenesis Enhanced glucose and aminoacid uptake Increased glycogen synthesis Conversion of glucose into fatty acids
B. Muscle	Enhanced glucose and aminoacid uptake Increased glycogen synthesis
C. Brain	Little or no effect on glucose metabolism
D. Adipose tissue	Increased fatty acids synthesis Inhibition of release of fatty acids from fat stores Increased glucose and aminoacid transport Enhanced glucose utilisation by tissues and thus spares fat
E. All tissues	Inhibition of protein catabolism Increased protein synthesis

Table 45.1 Metabolic effects of insulin on different tissues

These changes are hormone dependent. Oestrogen and progesterone facilitate the release of insulin and thus enhance the peripheral utilisation of glucose; fasting hypoglycaemia is therefore common in pregnancy. Also glucose readily crosses the placental barrier while insulin does not. Glucose from the mother is the main source of energy for fetal anabolic functions; its demand by the fetus is such that the glucose turnover rate in the normal adult is exceeded two or three fold. The net result is the reduction of blood glucose level to about 0.5 mmol/1 lower than for non-pregnant women.

Increased production of human placental lactogen (HPL), cortisol and prolactin occurs in pregnancy. These hormones exhibit contra-insulin effects especially in late pregnancy. The normal pregnant woman compensates this relative insulin resistance by producing more insulin and releasing it at increased rates. This explains why some pregnant diabetics may require increased doses of insulin as pregnancy advances.

In the diabetic patient, absence of insulin or insufficient production of insulin leads to under utilisation of glucose by the peripheral tissues, and the liver responds by increased breakdown of glycogen to glucose, so there is excess glucose (hyperglycaemia) in the circulation. Hyperglycaemia increases the osmotic pressure in the extracellular fluid space thus causing intracellular dehydration. Also the hyperosmotic extracellular glucose in the kidney causes diuresis and this leads to extracellular dehydration.

Persistent maternal hyperglycaemia causes fetal hyperglycaemia because of the ready movement of glucose from mother to fetus. The fetal response is fetal pancreatic hypertrophy and increased insulin production. It is this hyperinsulinaemia that is thought to cause the fetal macrosomia frequently seen in diabetic pregnancies as insulin is a major fetal growth factor. The mechanism for the unexplained fetal death that occurs suddenly in the third trimester is still unknown. Chronic fetal hyperglycaemia which causes altered glucose metabolism and subsequent hypoxia and acidosis, is thought to be the most likely predisposing factor. Other neonatal effects such as hypoglycaemia, respiratory distress syndrome and jaundice are also thought to be predisposed to by fetal hyperinsulinaemia.

CLINICAL FEATURES

Most of the pregnant diabetics would have been diagnosed before pregnancy; the others are asymptomatic and are picked up at routine blood glucose level screening in pregnancy or after an OGTT following glycosuria detected at routine antenatal clinics. A very small number in developing countries may be admitted as unbooked cases when they present with ketoacidosis in pregnancy.

The clinical signs and symptoms of diabetic ketoacidosis are due to marked dehydration, acidosis and electrolyte disturbances and are vomiting, polydipsia, polyuria, weakness, weight loss, abdominal pain, visual disturbances, leg cramps, Kussmaul's breathing (deep and rapid) and coma.

COMPLICATIONS

Most of the complications are less frequent in well controlled diabetes.

Maternal

Maternal ketoacidosis is rare but has grave consequences eg maternal and fetal mortality.
Infections are common especially urinary tract infections and vulvovaginal candidiasis. Respiratory tract, endometrial and wound infections are also more common.
Retinopathy and nephropathy are worsened during pregnancy. Pre-conceptual counselling is important in these patients.
Polyhydramnios is linked to fetal polyuria and is characteristic of poorly controlled diabetes.
Preterm labour is often associated with polyhydramnios.
The incidence of **pregnancy induced hypertension** is increased including that of pre-eclampsia.
Abortion is also more common as poorly controlled diabetics have a higher spontaneous miscarriage rate.

Fetal/Neonatal

Congenital malformations especially cardiac and neural tube defects are seen. Sacral agenesis is also associated with diabetic pregnancies.

Macrosomia. The infants of diabetic mothers (uncontrolled or badly controlled) are macrosomic with organomegaly and therefore prone to birth trauma.

Intrauterine growth restriction (IUGR). This is seen in diabetics with microvascular disease e.g. diabetic nephropathy.

Polycythaemia. They have polycythemia which predisposes them to hyperbilirubinaemia and neonatal jaundice.

Hypocalcaemia, hypoglycaemia and respiratory distress syndrome. These increase the perinatal mortality and morbidity.

MANAGEMENT

The management of a pregnant diabetic requires team work by the obstetrician, diabetic physician, paediatrician (neonatologist) and the dietician. Scrupulous attention to the control of diabetes at every stage of pregnancy is very important if the complications and perinatal mortality and morbidity are to be avoided and reduced to the barest minimum. It is therefore mandatory that all pregnant diabetics should be managed in a tertiary care centre where all facilities are available. Gestational diabetics may be controlled on diet alone but insulin should be started immediately if blood glucose levels become difficult to control. Oral hypoglycaemics are contraindicated in pregnancy as they cross the placenta and may cause fetal hypoglycaemia. Thus, pre-existing non-insulin dependent diabetic patients (NIDDM) should be placed on insulin if treatment is required during pregnancy.

Antenatal care

The patients are seen every two weeks up to 32 weeks and weekly thereafter up to delivery. They should be admitted any time there is a sign of infection or the control is thought to be less than perfect. Blood glucose level is repeatedly monitored, and in the case of newly diagnosed diabetics, it is wise to admit them for stabilisation. The insulin requirement is adjusted to suit the blood glucose level as necessary and the diabetic physician should be fully involved with this aspect of the management. The diet regime should be closely supervised and the patient should keep a chart of her urine glucose tests. Well motivated patients that can afford portable glucose meters (Fig. 45.1) should be encouraged to measure their blood glucose and bring a chart to hospital each visit. Such patients should have regular glucose level checks in the hospital laboratory as well to confirm the accuracy of the glucometer results. In general, blood glucose concentrations should be maintained between 4 and 6 mmol/l. Patients' co-operation is essential, thus they need to be well counselled about the significance of having good glucose control and the risks of poor control to themselves and their babies.

Glycosylated haemoglobin A (HbA1c) can be used to check the glucose control in the preceding 8 to 12 weeks. Some physicians prefer to use this monthly to monitor diabetic control. A higher than normal level of HbA1c suggests that the blood glucose levels in the preceding 8 to 12 weeks have been abnormally high. It is particularly useful in late bookers to have an idea of their previous control and also in preconception counselling of young diabetic women. In the latter group, if the HbA1c levels are raised the couple should be advised to postpone pregnancy until better control is achieved.

Blood glucose level, urinalysis, and mid-stream urine are checked at each visit. Oedema, hypertension, hydramnios and excessive weight gain are specially looked for at each visit.

An early ultrasound scan should be done in the first trimester if possible, in order to accurately date the pregnancy by measuring the crown-rump length of the fetus. A 16-20 week scan is mandatory to further establish maturity and to exclude fetal abnormality. Serial scans should be performed thereafter although the availability and costs of the scans will need to be taken into consideration. A suitable cost effective schedule could include 4-weekly scans till 32 weeks and fortnightly scans thereafter till delivery so that IUGR or macrosomia could be detected. Also the mother is asked to record fetal kicks as from 32 weeks, and antenatal cardiotocograph at weekly visits may help in preventing late fetal deaths. Biophysical profiles and Doppler ultrasound, if available, would also be useful in monitoring wellbeing in fetuses judged to be at risk. Whenever a decision to deliver is taken before 37 weeks or in a woman with uncertain dates, an amniocentesis under ultrasound guidance should be performed for Lecithin/sphingomyelin (L/S) ratio to exclude respiratory distress syndrome (RDS). This is because of the high risk of RDS in babies of diabetic mothers.

Labour

In the past we delivered the pregnant diabetic at 37 weeks by induction, and as many as 40-50 per cent ended up having a caesarean section. In recent times with very good control of diabetes, most of the patients go as far as 39 weeks or beyond and vaginal delivery is aimed at except where there are definite obstetric indications to the contrary. However, labour in pregnant diabetics is fully monitored and should not be allowed to be unduly prolonged; recourse to caesarean section is taken earlier in the interest of both mother and baby. Diabetic control in labour is best maintained by administration of 5 per cent glucose and insulin intravenously, the latter at a controlled rate by means of an infusion pump delivering soluble insulin 1-2 units per hour. The blood glucose is measured every hour and the rate of glucose infusion is varied accordingly. Where an infusion pump is not available half the dose of the morning requirement of insulin is given and infusion of 5 per cent glucose is set up. Thereafter a "sliding scale" with blood glucose level estimation is used in giving the necessary doses of insulin.

The paediatrician (neonatologist) must be present at the delivery and the baby is handed over to him or her for expert management as soon as it is delivered. Care in the baby intensive care unit will include early feeding to combat hypoglycaemia, venesection if the baby's PCV is greater than 70 per cent and treatment of hypocalcaemia and hyperbilirubinaemia as necessary.

Puerperium

The insulin requirement postpartum usually falls and episodes of maternal hypoglycaemia are not infrequent if care is not taken to monitor blood glucose levels regularly and adjust insulin doses appropriately. In most cases the insulin requirements drop by about 50%. There are no contraindications to breast feeding and it actually reduces insulin requirements. Women with *gestational diabetes* should have a glucose tolerance test 6 weeks after delivery as they are at risk of maturity onset diabetes mellitus.

PROGNOSIS

Ideally diabetes should be well controlled before conception. It is now believed that the incidence of malformation is higher in women whose diabetes pre-conception was badly controlled and remained so in the first trimester. Also the prevalence of early abortion is high in this group of patients, and some who have severe disease would remain infertile. Those with stigmata of complicated severe diabetic pathology such as retinopathy, renal pathology and peripheral angioneuropathies should be

advised against pregnancy as their condition would worsen and fetal and maternal outcomes are very poor.

With the advent of insulin and generally improved care of pregnant diabetics, the maternal and fetal outcomes are excellent. However, such patients are advised to limit their family size as repeated pregnancies would worsen their condition and reduce their life span. Permanent contraception in the form of tubal ligation or vasectomy should be offered after 2 or 3 children and judicious use of oral contraceptives and intrauterine devices for short term family planning to space the children is advisable. Barrier methods and progesterone only pills can also be used although the higher failure rates associated with their use may not be acceptable.

Bibliography and suggested further reading:

Lind, T. (1984) Commentary: Antenatal screening for diabetes mellitus. Br. J. Obst. Gynaec. 91: 833.

Abudu, O., Kuti J. (1987) Screening for diabetes in pregnancy in a Nigerian population with a high perinatal mortality rate. Asia Oceania J. Obstet Gynecol. 13:305.

Brumfield, C.G., Huddleston, J.F. (1984) The management of diabetic ketoacidosis in pregnancy. Clinical Obstet. Gynaecol. 27:50.

Kuti, J.A., Ohwovoriole, A., Abudu, 0., Johnson T.O. (1985) Diabetes mellitus and pregnancy in a Nigerian Teaching Hospital. Nig. Quarterly Journal of Hosp. Med. 3:51

Kuti, J.A., Ohwovoriole, A., Abudu, 0., Johnson T.O. (1982) Haemoglobin A_1 levels in Nigerians. Nig. Quarterly Journal of Hosp. Med. 1:21.

Nelson-Piercy, C. (1997) Diabetes. *In*: Nelson-Piercy, C. (ed.) Handbook of Obstetric Medicine, 1st ed. Oxford: Isis Medical Media.

Enkin, M., Keirse, M.J.N.C., Neilson, J., Crowther, C., Duley, L., Hodnett, E., Hofmeyr, J. (2000) Diabetes in pregnancy. *In*: Enkin, M., Keirse, M.J.N.C., Neilson, J., Crowther, C., Duley, L., Hodnett, E., Hofmeyr, J. (eds.) A guide to effective care in pregnancy and childbirth, 3rd ed. Oxford: Oxford University Press.